State of California

SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS

NOTICE OF PUBLIC MEETING

The Scientific Review Panel on Toxic Air Contaminants (SRP), established pursuant to Health and Safety Code section 39670, will hold a public meeting at the time and place set forth below.

DATE: Thursday, January 23, 1992

TIME: 9:30 a.m.

PLACE: San Francisco Conference Center
Suite E
1240 Old Bayshore Highway
Burlingame, CA

AGENDA

1. Consideration of Air Resources Board (ARB)/Office of Environmental Health Hazard Assessment (OEHHA) Report Regarding the Identification of 1,3-Butadiene as a Toxic Air Contaminant

2. ARB Response to SRP Request to Evaluate Environmental Tobacco Smoke as a Toxic Air Contaminant

3. Discussion of Future Meeting Dates

INFORMATION

The SRP is charged with reviewing for scientific adequacy the risk assessment reports prepared by the ARB, OEHHA, and Department of Food and Agriculture. These reports are prepared for the purpose of determining whether a substance or pesticide should be identified as a toxic air contaminant. Written comments or submissions from the public regarding a report submitted to the SRP for review which are received pursuant to the requirements specified in the report notice will be considered by the SRP. Information regarding submission of comments or other information is provided when the report is released for public review. The SRP does not accept written or oral comments from the public at its meetings. For further information on the meeting or to obtain the ARB report, please contact:

Bruce Oulrey
Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, CA 95812
Telephone: (916) 323-8711

SMOKING IS NOT PERMITTED AT MEETINGS OF THE SCIENTIFIC REVIEW PANEL

SCIENTIFIC REVIEW PANEL

Meeting: January 23, 19 92

Guests

NAME	TITLE	ORGANIZATION
SUD PERSSON	CONSULTANT	SELF
[illegible] HARDING-BARLOW	CONSULTANT	Self.
Katrina Hollins	Typesetter	EAOMX
Gary Cook	Director, Business Devel. Chromalab	Chromalab

REGISTERING ON THIS ATTENDANCE LIST IS VOLUNTARY. ALL PERSONS MAY ATTEND THIS MEETING WHETHER OR NOT THEY REGISTER ON THIS SHEET.

Proposed Draft 1/21/92

Findings of the Scientific Review Panel on
THE REPORT ON 1,3-BUTADIENE
As Adopted at the Panel's January 23, 1992 Meeting

In accordance with the provisions of Health and Safety Code Section 39661, the Scientific Review Panel (SRP) has reviewed the report ("Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant") of the staffs of the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA) on the public exposure to, and health effects of 1,3-butadiene. The Panel also reviewed the public comments received on this report. Based on this review, the SRP finds that the report on 1,3-butadiene is without serious deficiencies and agrees with the staffs of the ARB and OEHHA that:

1. There is evidence that exposure to 1,3-butadiene results in animal carcinogenicity and possible human carcinogenicity. The International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (US EPA) have classified 1,3-butadiene as a "possible" and "probable" human carcinogen, respectively, on the basis of sufficient evidence for carcinogenicity in animals and inadequate evidence in humans.

2. Because 1,3-butadiene is listed as a hazardous air pollutant under Section 112 of the United States Clean Air Act of 1990, identification of 1,3-butadiene as a toxic air contaminant is required by the California Health and Safety Code Section 39655.

3. Based on available scientific information, a level of 1,3-butadiene exposure below which no carcinogenic effects are anticipated cannot be identified.

4. Based on a health protective interpretation of the available scientific evidence, the upper bound of the lifetime excess cancer risk resulting from 1,3-butadiene exposure ranges from 0.0098 to 0.8 per part per million (ppm), or 4.5×10^{-6} to 3.6×10^{-4} per microgram per cubic meter (ug/m^3). The best value of the upper bound of risk is 0.37 per ppm, or 1.6×10^{-4} per ug/m^3. Appendix I compares the best value of the upper bound 1,3-butadiene cancer unit risk with those of other compounds reviewed by the SRP. These 95 percent upper bound lifetime risk estimates are health-protective estimates; the actual risk may be significantly lower.

5. Mobile sources are responsible for the majority of the identified emissions of 1,3-butadiene. Stationary area and point sources contribute to ambient concentrations of 1,3-butadiene during petroleum refining, fuel combustion, production of certain chemicals, and the manufacturing of styrene-butadiene copolymer products.

6. Based on data collected by the ARB's ambient toxic air contaminant monitoring network, the estimated mean annual population-weighted outdoor ambient exposure for California is 0.37 ppbv (0.82 ug/m^3).

7. Based on the ARB emission inventory, areas that may be expected to have 1,3-butadiene levels higher than the mean statewide concentration are near facilities using 1,3-butadiene for the production of resins and polymers, synthetic rubber manufacturing facilities, chemical production facilities, petroleum refineries, stationary fuel combustion sources, and congested freeways. New data from the AB2588 Air Toxics "Hot Spots" emissions reporting program should be used to evaluate "hot spot" exposures if 1,3-butadiene is identified as a toxic air contaminant.

8. Based on its gas-phase reactivity with the hydroxyl radical, ozone, and the nitrate radical, 1,3-butadiene's estimated tropospheric lifetime ranges from a few hours to about 12 hours.

9. Limited indoor monitoring for 1,3-butadiene suggest that individuals exposed to a heavy smoking environment may be exposed to higher concentrations of 1,3-butadiene indoors than outdoors.

10. Studies of animals exposed to parts-per-million concentrations of 1,3-butadiene indicate that 1,3-butadiene is taken up rapidly by the body and distributed with metabolites to all tissues. This distribution can result in cancer in multiple sites, including the heart, lung, mammary gland, ovaries, forestomach, liver, pancreas, thyroid, testes, and hematopoietic system. It is one of only two chemicals (the other being the fungicide Captafol) known to induce cancer in the heart of laboratory animals. Epidemiological studies of production workers exposed to 1,3-butadiene show an increased risk of death from hematologic neoplasms, especially leukemia and other lymphomas. Adverse health effects other than cancer are not expected to occur at mean statewide outdoor ambient concentrations.

11. Based on the OEHHA staff's best value cancer unit risk of 1.6×10^{-4} per ug/m^3, and the ARB staff's population-weighted outdoor ambient exposure of 0.37 ppbv (0.82 ug/m^3), up to 131 potential excess cancers per million are predicted if exposed to this level over a 70 year lifetime. This corresponds to an excess cancer burden of up to 3,936 cancers statewide (based on a population of 30 million people).

12. Based on available scientific evidence indicating that 1,3-butadiene is an animal and a possible human carcinogen, we conclude that 1,3-butadiene should be identified as a toxic air contaminant.

For these reasons, we agree with the ARB staff recommendation to its Board that 1,3-butadiene be listed by the ARB as a toxic air contaminant.

I certify that the above is a
true and correct copy of the
findings adopted by the
Scientific Review Panel on
January 23, 1992

_____

Dr. James N. Pitts, Jr.
Chairman, SRP

APPENDIX I

COMPOUNDS APPROVED BY THE SCIENTIFIC REVIEW PANEL FROM 1984 TO 1992
(in order of cancer potency)

Compound	Unit Risk $(ug/m^3)^{-1}$	Unit Risk $(ppbv)^{-1}$
Dioxins	$3.8x10^{1}$	Particulate Matter
Chromium VI	$1.4x10^{-1}$	Particulate Matter
Cadmium	$4.2x10^{-3}$	Particulate Matter
Inorganic Arsenic	$3.3x10^{-3}$	Particulate Matter
Nickel	$2.6x10^{-4}$	Particulate Matter
1,3-Butadiene	$\mathbf{1.6x10^{-4}}$	$\mathbf{3.7x10^{-4}}$
Ethylene Oxide	$8.8x10^{-5}$	$1.6x10^{-4}$
Vinyl Chloride	$7.8x10^{-5}$	$2.0x10^{-4}$
Ethylene Dibromide	$7.1x10^{-5}$	$5.5x10^{-4}$
Carbon Tetrachloride	$4.2x10^{-5}$	$2.6x10^{-4}$
Benzene	$2.9x10^{-5}$	$9.3x10^{-5}$
Ethylene Dichloride	$2.2x10^{-5}$	$8.9x10^{-5}$
Perchloroethylene	$8.0x10^{-6}$	$5.4x10^{-5}$
Formaldehyde	$6.0x10^{-6}$	$7.0x10^{-6}$
Chloroform	$5.3x10^{-6}$	$2.6x10^{-5}$
Trichloroethylene	$2.0x10^{-6}$	$1.1x10^{-5}$
Methylene Chloride	$1.0x10^{-6}$	$3.5x10^{-6}$
[Asbestos	$1.9x10^{-4}$ per 100 fiber/m^3]	

STATE OF CALIFORNIA
AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

PETE WILSON, Governor

January 3, 1992

Dear Scientific Review Panel Member:

The Scientific Review Panel ("the Panel") version of the report to the Air Resources Board (ARB) on the Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant is enclosed for your review. The report, prepared by the ARB and the Office of Environmental Health Hazard Assessment (OEHHA) staffs pursuant to Health and Safety Code Section 39650 et seq., includes Parts A, B, C and an Executive Summary. Part A, prepared by the ARB staff, includes a review of the uses, emissions, and ambient concentrations of 1,3-butadiene in California. Part B, prepared by the OEHHA staff, evaluates the health effects of 1,3-butadiene. Part C contains public comments and ARB/OEHHA staffs' responses to those comments. The Executive Summary summarizes the exposure and toxicological information in Parts A and B. Based on the exposure and toxicological information in the report, the staff is recommending that 1,3-butadiene be identified as a toxic air contaminant.

According to Health and Safety Code Section 39650 et seq., the Panel is to submit written findings to the ARB within 45 days of receipt of this report. In consideration of mailing time, we estimate that the findings are due February 24, 1992. If needed, the Panel may petition the ARB for a 15-working-day extension.

I understand that you will be reviewing this report at your January 23, 1992, meeting. The public had an opportunity to review and comment on an earlier version of this report during a public comment period (February 7 through March 22, 1991) and at a public workshop (March 27, 1991). The public has also commented on this version (November 1 through December 6, 1991). The ARB and OEHHA staffs will respond to the public comments on this version of the report at the Panel's meeting.

If you have any questions, please contact Bruce Oulrey at (916) 445-3187.

Sincerely,

Donald J. Ames for

Peter D. Venturini, Chief
Stationary Source Division

Enclosure

cc: Assemblywoman Sally Tanner, Chairwoman
Environmental Safety and Toxic Materials

Senator Art Torres, Chairman
Senate Toxics and Public Safety Management Committee

Dr. George Alexeeff, OEHHA

Bruce Oulrey, ARB

bcc: William Lockett (w/Enclosure)✓
Don Ames
Leslie Krinsk
Genevieve Shiroma
Joan Denton
Kelly Hughes
1,3-butadiene file

January 22, 1992

OEHHA STAFF-RECOMMENDED CHANGES
TO PART B OF THE 1,3-BUTADIENE TSD

1. Change the sentence regarding Checkoway and Williams in the first paragraph of Section 3.6 ("In addition ... reported." [p. 3-20]) to read:

"In addition, Checkoway and Williams (1982) observed statistical associations of blood parameters with butadiene exposure at a facility where excess leukemia and lymphoma had been reported.

2a. After the first 2 sentences of the 3rd paragraph on p. 3-24 ("To elucidate .... did not have cancer."), add:

" A log transformation of exposure data was used to classify workers into high- and low-exposure categories."

2b. Then, after "... not to styrene." add:

" This study's results appear sensitive to the choice of exposure classification scheme. In addition, "

3. In last paragraph of Section 3 (p. 3-28), change:

"Butadiene production workers, those with routine exposure to butadiene and people who worked at SBR or butadiene-manufacturing facilities during WWII have been at higher risk for these cancers."

to read:

"Butadiene production workers and those with routine exposure to butadiene have been at higher risk for these cancers. High levels of butadiene during WWII in certain facilities may have contributed to this excess risk, although elevated cancer rates specific to WWII workers have not been conclusively demonstrated."

4. Add an extension to Section 5.3, and a Table 5-1b, comparing upper bounds on observations in epidemiologic studies with upper-bound predicted observations based on "Mouse II" (Melnick et al. 1990) data.

January 22, 1992

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT (OEHHA) STAFF RESPONSES TO PUBLIC COMMENTS ON THE SCIENTIFIC REVIEW PANEL (SRP) VERSION DRAFT RELEASED SEPTEMBER 1991 OF THE TECHNICAL SUPPORT DOCUMENT (TSD) FOR THE PROPOSED IDENTIFICATION OF 1,3-BUTADIENE AS A TOXIC AIR CONTAMINANT

Comments from the Chemical Manufacturers Association (CMA)

1. Comment: OEHHA's "best estimate" of the human cancer potency of butadiene (BD), 0.37/ppm, based on lung tumors in female mice, is inconsistent with the results of epidemiologic studies. It should be noted that every BD epidemiology study conducted thus far has observed a deficit of lung tumors. OEHHA has significantly overstated the human cancer risks arising from butadiene exposure. Thomas B. Starr has found the observed cancer rates in studies of BD-exposed workers to be inconsistent ($p = 6.9 \times 10^{-44}$) with the cancer rate predicted using the 0.37/ppm potency slope (despite methodological flaws in one epidemiologic study that would tend to bias the results toward consistency). John F. Acquavella has obtained similar results in a consistency check of a similar risk assessment. OEHHA's consistency check of its risk assessment is based, without justification, upon potency estimates only up to 0.089/ppm. It would have been far more appropriate to perform a consistency check using OEHHA's separate rat-based and mouse-based "best estimates" of potency. In contrast to the mouse-based estimate, OEHHA's rat-based potency estimate yields predicted numbers of cancer deaths that are not demonstrably inconsistent with those observed. (CMA, comments dated December 6, 1991, pp. i, 2-3, and Appendices II and IV).

Response: The TSD's risk assessment is based upon the newest bioassay (Melnick et al. 1990, or "NTP II"). OEHHA staff did not update the document's consistency check (Part B, Section 5.3) when the new data were incorporated into the risk assessment. However, Staff believe that Dr. Starr's analysis is flawed for the following reasons:

1) It compares upper bound rodent estimates to central tendency human estimates which should overpredict by definition.
2) Concordance of site-to-site extrapolation is not expected across species.
3) Overpredictions may be high for lung-to-lung comparisons for the one study analyzed, but not for total cancer comparisons across species or for other valid comparisons.
4) The predominantly male worker studies would be expected to underpredict population estimates.
5) The epidemiologic studies are generally conceded to be lacking sufficient exposure detail to be quantitatively useful.
6) In response to this comment, staff have prepared an additional "consistency check" analysis for inclusion in the document.

Dr. Starr's analysis compares predictions from a mouse-based upper bound potency estimate with actual observations in one epidemiological

study of humans. Upper bound estimates are designed to predict a value which is not likely to be exceeded, not the median or mean cancer rate. Since the observed cancer rate was not exceeded, the upper bound estimate may be consistent. Dr. Starr concluded that when compared with observed human lung cancers, the upper bound estimate for the mouse was inconsistent while the upper bound estimate for the rat was consistent. However, OEHHA staff believe that based on the comparison made, the upper bound estimate for the rat would be an underprediction of a human population risk since the Starr analysis compares the rodent upper bound to the central tendency in one worker study. In the previous OEHHA analysis (Table 5-1), the maximum likelihood estimate (MLE) from the mouse I study is compared to measures of central tendency from two worker studies. In OEHHA's additional analysis the mouse upper bound estimate is compared to upper bound estimates for two human studies.

Butadiene has been shown to be a multisite carcinogen in animal studies. It produces cancer of the heart, lung, liver, ovaries, forestomach, hematopoietic system and mammary gland. Staff believe that it may act at many sites in humans as well. The female mouse lung was the most sensitive site and sex in the "mouse II" study. It was chosen for the best value since the response at this site appears scientifically valid and consistent with genotoxicity and cancer information on butadiene. The female lung also appears to be the best site to choose for risk assessment. This site exhibited a fairly low background rate (8%) in the controls. It was the only site that was significantly elevated in the lowest dose tested in the study (6.25 ppm). Thus, there are fewer competing risks which confound the lung potency estimate in mice. Due to the compound's lack of site specificity, we do not expect lung cancer produced in mice to be directly correlated with lung cancer rates in humans. OEHHA staff believe that the best comparisons are based on total cancers produced in human studies or significant excesses found in human studies. In OEHHA's most recent analysis, comparisons are made with the best upper bound value to overall human cancers and significantly increased rates of hematopoietic cancers for two epidemiologic studies.

Dr. Starr's analysis shows a 1.3- to 2.8-fold overprediction of all cancers in a worker study. OEHHA staff believe that this indicates that the mouse upper bound estimate is not very inconsistent with the human estimates. Although elevated lung tumor rates have not been observed in exposed humans, there is epidemiologic evidence that butadiene may cause lymphatic cancers in humans (and such cancers have been seen in mice). Butadiene may have caused tumors at other sites (including the lung) in humans that have gone undetected due to the limited power of epidemiologic studies. OEHHA staff believe that comparison of the best value in animal studies to observed excess cancer rates in humans is also a valid consistency check, and such a comparison was made in the additional OEHHA analysis.

There are several reasons why a worker cohort may underpredict the risk for the general population. First, the well-known "healthy worker effect" may have muted the apparent cancer potency of BD in these studies. Second, the age of exposure may affect the potency estimate and the site of tumor development. While the animals were exposed from youth, humans in the epidemiologic studies were exposed as adults. Young animals have a

better likelihood of developing cancer due to the latency for cancer. Furthermore it is possible that younger animals exhibit a different sensitivity to butadiene exposure and that different sites may exhibit cancer due to the development process. Third, rat and mouse studies indicate that females tend to be more sensitive than males to butadiene exposure. One must be concerned about the susceptibility of the young and of women, since they are generally not represented in worker studies. Other factors may also have muted the potency apparent from the epidemiologic studies (see Sections 3.6 and 5.3 of Part B of the TSD).

Data from epidemiologic studies are sometimes used for quantitative cancer risk assessment. The epidemiologic data regarding persons exposed to butadiene are not adequate for this purpose. Few exposure data are available (for BD and other workplace chemicals), and most studies have very limited power to measure a dose-response association. Nevertheless, when epidemiologic studies are used for risk assessment, the reported "best" potency estimates are usually upper bounds (partly to account for the potential non-representativeness of the sample). Thus, comparisons such as those in Dr. Starr's analysis should consider upper bounds on the tumor incidences observed in epidemiologic studies. OEHHA staff considered such upper bounds in preparing the extension to Section 5.3 of the TSD.

The OEHHA reanalysis is summarized in Table 5-1b. In this instance comparisons are made between the OEHHA best value for the upper bound to an upper bound on the observed value in two epidemiologic studies. In the reanalysis all cancers were considered as well as elevated rates of lymphopoietic cancer. An adjustment was made for time and age of exposure (CC Brown and KC Chu (1983) A new method for the analysis of cohort studies: implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. Environmental Health Perspectives 50:293-308). The analysis compares upper bound of predicted plus background with upper bound observed. The analysis indicates reasonably good consistency between animal-based estimates and human observations.

2. Comment: The epidemiology review in the SRP version of the TSD selectively highlights positive findings, neglects important negative findings, and relies on a number of unproven assumptions. These assumptions include a uniform reduction in industrial BD exposure after 1945, and a lack of correlation between employment duration and cumulative exposure. The reduction in exposure assumption is based only on process changes in polymerization areas of styrene-butadiene rubber (SBR) plants (rather than measurements, which only began in the 1970s), and there were no corresponding process changes in the studied BD monomer plant. The review fails to note that findings of a base cohort study conflict with a nested (lymphopoietic cancer) case-control study (CMA, Appendix IV, pp. 1-3).

Response: First, it should be noted that the document's risk assessment does not rely on epidemiology. The document's epidemiology review is designed to highlight positive findings, and gives consideration to important negative findings. The review mentions, rather than "relies on," the reduction in BD exposure after 1945. If a desire to reduce workplace BD exposure was a driving force behind changes in production processes, it is likely that exposure of all workers, including non-polymerization

workers, was reduced. The TSD does not rely upon a uniform reduction in exposure after World War II. The review reports both the negative findings of the base cohort study and the positive finding of the nested case-control study mentioned in the comment. The review also describes a job classification-based analysis of the cohort data, which had positive findings and prompted the nested case-control study. Many caveats regarding interpretation of these findings are communicated in the review. One must also keep in mind that negative epidemiologic studies do not necessarily contradict positive human or animal studies. Instead, the negative nature of a study may be the result of confounding factors or lack of power of the epidemiologic study.

3. Comment: The conclusion of a carcinogenic effect among workers employed prior to 1946 is not consistent with the available epidemiologic data (CMA, Appendix IV, pp. 3-6).

Response: The comment makes good points regarding the separate analyses of workers employed prior to 1946 (during World War II). Many of these workers had only short term exposure, albeit at high levels. The authors of one analysis note that their mortality rate comparisons are *a posteriori* and only find significant differences with a one-tail test (Lemen et al. 1990, p. 105). Since the World War II worker analyses are limited, OEHHA staff have prepared a suggested modification of the conclusion in the TSD regarding those workers. Nevertheless, the high levels of butadiene in World War II plants certainly imposed cancer risks upon the exposed workers. Scientists agree that BD is a carcinogen, that metabolites of BD may act directly on DNA, and that there is no known dose threshold for BD carcinogenesis. Epidemiological studies have not clearly detected increased cancer rates among World War II butadiene and SBR workers. Given the general limitations of occupational cancer epidemiology, this is not unexpected.

4. Comment: TSD's authors mention that the lymphopoietic cancer findings from the Matanoski et al. cohort study are of limited usefulness because of the omission of early (World War II) workers. However, data from a subset of the plants considered in that study, where early workers were completely enumerated, show no excesses (and borderline significant deficits) of lymphopoietic cancers, lymphosarcoma and leukemia (CMA, Appendix IV, pp. 6-7).

Response: The TSD mentions the omission of some World War II workers as a factor that should be considered in interpreting Matanoski et al.'s results. Although the data presented in the comment do bear on the issue, the effects of this omission remain unknown. The fact that potentially useful person-years were not included in the study remains a valid concern.

5. Comment: Another unproven assumption relied upon by the TSD is biological consistency of varied lymphopoietic cancer findings across studies. The document dismisses the criticism that variation in health endpoints across studies detracts from finding a causal relationship between BD and lymphopoietic cancer. In this regard, the TSD's authors should consider and respond to certain testimony before the U.S. Occupational Safety and Health Administration by P. Cole. The document suggests that individual lymphopoietic cancers are related tumors. Yet, if

this were so, one would expect to see general lymphopoietic cancer excesses (for all sites) rather than the variable findings for specific lymphopoietic cancers actually observed. The document cites diagnostic overlap and changing nomenclature over time in disregarding the heterogeneity of the lymphopoietic cancer findings. This is not a credible explanation because diagnostic overlap would also have occurred in the comparison populations for the cohort studies. Also, diagnostic variability differs by type of lymphopoietic cancer, and will have little effect on cancers with a high percent confirmation. Diagnostic specificity has improved with time, and most of the deaths occurred in the last 10-15 years of the studies (CMA, Appendix IV, pp. 7-9).

Response: The comment enumerates several reasons for not relying on human studies. Clearly, uncertainties exist in using human studies. This requires the risk assessor to consider those uncertainties and weigh them against the uncertainties in using animal studies. Part B of the TSD does so, and applies the epidemiologic data in a supportive manner. The TSD's epidemiology review does consider the possibility that the various blood and lymph cell cancers may be related. The TSD's animal data-based risk assessment does not rely on an assumption of biological consistency among these tumors, however. There are rational bases for considering the cancers to be related. Some of these are cited in Section 3.6.3 of the TSD's Part B. That general increases in lymphopoietic cancers were not seen may be a reflection of the insensitivity of the epidemiologic studies. These studies considered occupationally exposed populations of which only small subsets had high-level exposure to butadiene. If the blood and lymph cancers are indeed related (and related to BD), chaotic variations within the "grouped cancer" incidences might cause different specific cancers to appear as significantly elevated in different studies, resulting in the observed heterogeneity of findings. Finally, if diagnostic overlap or misclassification occurred in both an exposed group and a comparison population, the results of studies would be biased towards the null hypotheses (no effect of exposure). Thus any changes over time in diagnostic specificity should be a matter of concern.

OEHHA staff have considered the referenced testimony of Dr. Cole. It highlights evidence for heterogeneous etiology of heterogeneous lympho-hematopoietic cancers ("LHC" in the testimony, or "lymphopoietic cancers" here). Although such cancers are morphologically (and thus etiologically) distinct, it does not follow that butadiene will necessarily be associated with either (1) specific lymphopoietic cancers or (2) all lymphopoietic cancers in studies of worker cohorts. First, one must remember the limited nature of such studies and the uncertainties involved with relying on them. Second, one should note that all cancers, including lymphopoietic cancers, are generally though to have multiple causes. Environmental carcinogens may act upon or in concert with varying genomes to produce varying tumors. Dr. Cole gives examples of varying genetic susceptibilities to leukemias. Environmental carcinogens may act upon or in concert with different environmental (or lifestyle-associated) chemicals or stresses (such as viruses or other disease organisms, or immune-suppressing behaviors) to produce different tumors. It is possible that butadiene may facilitate the development of different blood or lymph system tumors in persons of different genomes or in cohorts of different experience. Clusters of differently-susceptible individuals may thus be found in different

occupational cohort studies. In the epidemiologic studies discussed in the TSD, butadiene may have acted synergistically with different confounding genetic susceptibilities, workplace exposures, or viruses. Thus one cannot rule out a causal role for butadiene.

All lymphopoietic cancers derive from the same embryonic tissue germ layer (mesoderm) and in such cancers similar types of genes may be active. These genes may be similarly susceptible to carcinogens such as butadiene, with BD insult leading to morphologically different lymphopoietic cancers under different circumstances. However, as noted above, the data regarding chronic exposure of humans to BD are limited and the TSD does not rely on these data for the risk assessment. It is possible that confounding factors largely explain the increased cancer rates found in the epidemiologic studies discussed in Part B's review. These were studies of occupational cohorts, however, and more-susceptible subgroups of humans are likely to exist in the general population, with exposure (albeit lower-level exposure) throughout life.

6. Comment: The findings from an SBR workers lymphopoietic cancer case-control study are irreconcilable with findings for the cohort study of the same population. These two studies should be evaluated together, and emphasis should be placed on finding an interpretation for the case-control results that is consistent with the lack of a leukemia excess for the SBR worker cohort overall. The case-control study in particular should be examined critically; there appears to be a large random error component there, making its results sensitive to varying exposure classification schemes (CMA, Appendix IV, pp. 9-15).

Response: The two study reports are not irreconcilable because they are based on the same data. The TSD evaluates them in sequence. It is not surprising for a case-control study to show a significant effect where a cohort study does not, because case-control studies are ordinarily more powerful than cohort studies. The TSD mentions the 1989 observation by Acquavella (who prepared this part of CMA's comments) that an abnormally low leukemia rate among unexposed workers may have caused the case-control study's high odds ratio. In response to this comment, OEHHA staff have prepared additions to the TSD's examination of the case-control study, to indicate that the study's results were sensitive to the choice of exposure classification scheme and that a log transformation was used. The commenter, although critical of the classification scheme, notes that the log transformation decreased the skewness of the exposure data. Although it may not have produced a normal distribution, such a transformation is an accepted technique in statistical analysis.

7. Comment: Although the TSD mentions that Checkoway and Williams (1982) attributed hematological abnormalities to butadiene exposure in a cohort of SBR workers, this statement is not true since the values for the highest exposed group were all within the normal range. The investigators concluded that there was no significant difference between the two exposure groups in their study. Thus the TSD's citation of this study is misleading (CMA, Appendix IV, pp. 1, 15-16).

Response: Checkoway and Williams (1982) did find that changes in blood parameters were associated with butadiene exposure. However, the comment

points out that the word "abnormalities" can rightly be considered inappropriate for describing those changes; the investigators themselves noted that there was no striking indication of bone marrow toxicity related to exposure (1982, p. 168). Checkoway and Williams also noted that causality could not be inferred directly from their study (*Ibid.*). Thus, OEHHA staff have prepared a modification of the TSD, to remove the words "abnormalities" and "attributed" from the summary sentence near the beginning of Section 3.6 of Part B. A more complete description of the Checkoway and Williams study may be found in Section 3.6.3, as released.

8. Comment: The TSD's epidemiology review neglected findings for white production workers and for white and black mechanical workers in its review of Matanoski et al. (1990). These findings are important because process and mechanical workers have frequent opportunity for butadiene exposure. The findings for mechanical workers are particularly important because of these workers' opportunity for intermittent peak exposures, and because the TSD's authors have drawn an analogy between certain peak exposure mouse studies and findings from epidemiology. The omitted findings show no elevation of lymphopoietic or all cancers and are thus inconsistent with the analogy to the high exposure/short-time mouse studies. Also, a more appropriate analysis of the Matanoski et al. (1990) data would have shown that there was not an overall lymphoma excess for all production workers (CMA, Appendix IV, pp. 16-18).

Response: OEHHA staff have noted that the stop exposure studies of Melnick et al. (1990) in mice indicate that short-term higher exposures to BD may result in greater tumor incidences than longer-term lower exposures (see Part C of the TSD, pp. OEHHA C-18 to OEHHA C-19, International Institute of Synthetic Rubber Producers, Inc. [IISRP] comment 5 [and response]). Nevertheless, we would not expect to see elevated incidence rates in every "peak exposed" subcohort of every epidemiologic study.

The "mechanical workers" described in the comment are considered maintenance workers by Matanoski et al (1990). The comment cites a report by Fajen et al. (JM Fajen, DR Roberts, LJ Ungers and ER Krishnan (1990) Occupational exposure of workers to 1,3-butadiene. Environmental Health Perspectives 86:11-18) as indicating that these workers have had opportunity for intermittent peak exposures. However, these exposures may have been few and far between. Based on full-shift personal samples, Fajen et al. found that maintenance workers had the second-lowest geometric mean butadiene exposure (0.122 ppm) among the six job categories with some samples showing exposure in excess of 10 ppm. Although some workers had some days of peak exposure, continuous high exposure for several weeks or months was not documented, and these workers' exposure was not closely analogous to the mouse exposures. In addition, it is not clear that all maintenance workers were similarly assigned to peak exposure tasks.

The TSD's analysis of the Matanoski et al. (1990) data clearly notes that no cancer SMR was significant when the total cohort was analyzed (see Table 3-4, p. 3-27).

9. Comment: The TSD's epidemiology review gives undue attention to studies of tire manufacturing populations in which solvents have previously been associated with elevated rates of lymphatic leukemia. The TSD's

authors have chosen to disregard the earlier comment that studies of tire manufacturing populations are essentially irrelevant for butadiene since butadiene is not liberated during tire manufacturing. Only one of these studies had a subcohort employed in an SBR "synthetic plant," and for these workers it is unclear whether exposures resembled SBR production plants. Further studies by the research group there attributed the elevated leukemia findings to solvent, rather than BD, exposure. The TSD should not confuse the evaluation of BD by discussing tire manufacturing studies in detail (CMA, Appendix IV, pp. 1, 18-19).

Response: As OEHHA staff have previously noted in responding to the earlier comment regarding tire manufacturing populations (see Part C, pp. OEHHA C-17 to OEHHA C-19, IISRP comments 3 and 6), the TSD only presents results from groups of workers involved with rubber synthesis. Whether or not the exposures in the synthetic plant in the tire manufacturing facility resembled those in SBR production plants, the workers there were almost certainly exposed to butadiene. The report of "further studies" referenced by the comment (H Checkoway, T Wilcosky, P Wolf and H Tyroler (1984) An evaluation of the associations of leukemia and rubber industry solvent exposures. Am J Industrial Medicine 5:239-234) is limited. This report uses "data from a small case-control study of lymphocytic leukemia" (p. 239): it does not separately address the synthetic plant, and does not address butadiene.

10. Comment: The TSD's interpretation of Ott et al. (1980)'s findings in SB latex workers reflects an unwillingness to accept negative findings from any study. There were no leukemias among 391 such workers. The contention that this finding is not reliable because "OEHHA staff were not able to confirm that this OTG was the only one in which butadiene exposure occurred" indicates a biased perspective regarding this study. Even if there were other BD-exposed workers in this study, they would not affect the negative findings in SB latex workers (CMA, Appendix IV, pp. 19-20).

Response: The epidemiology review in the TSD clearly reports the negative findings (zero cases of leukemia) in the SB latex group. No biased perspective is reflected in this review. Only 391 workers were in the SB latex group, but elevated SMRs for leukemia and for lymphatic and hematopoietic neoplasms were seen for the whole 2,904-worker cohort. It is thus logical to inquire whether some of the non-SB latex workers were exposed to butadiene (see Part C, pp. OEHHA C-17 to OEHHA C-20, IISRP comments 3, 6 and 8).

11. Comment: OEHHA should use more data for its best estimate of likely human cancer risk. The "best estimate" presented in the TSD is an upper bound based on several "worst case" assumptions that are implicit in generic cancer risk assessment guidelines. The collective use of these assumptions is not realistic and does not provide a reasonable basis for estimating likely excess human cancer deaths from exposure to BD in ambient air (CMA, p. 1).

Response: OEHHA staff believe that the methods used in the TSD are reasonable, and represent prudent public health practice. The assumptions and choices made in the TSD are indeed made in accordance with generic, or default, guidelines (see State of California (1985) Guidelines for Chemical

Carcinogen Risk Assessments and Their Scientific Rationale. Issued by: Health and Welfare Agency, Department of Health Services). The assumptions suggested by these guidelines and used in the TSD reflect health protection and plausible (rather than "worst case") scenarios.

12. Comment: OEHHA's reasons for basing its best estimate of human cancer risks on the B6C3F1 mouse data are not valid. The assertions that the mouse study was repeated at lower doses with consistent results and that the mouse data are available in greater detail do not provide a valid basis for preferring the mouse data. Stuart Z. Cagen has addressed similar arguments advanced by the National Institute for Occupational Safety and Health.

Contrary to OEHHA's assertion, the epidemiologic data do not provide any basis for preferring the mouse over the rat data. The increased incidence of lymphocytic and hematopoietic cancers in B6C3F1 mice has been observed only at relatively high doses and may reflect the presence of an endogenous retrovirus not present in humans. It is extremely doubtful that these tumors are relevant to an assessment of potential human cancer risks from exposure to ppb levels of BD in ambient air.

OEHHA would be more objective to acknowledge that all three cancer bioassays are adequate for risk assessment, and that the risk assessor has the task of choosing the species which provides the best model. The available data on butadiene metabolism and mechanism of action indicate that the B6C3F1 mouse is uniquely susceptible to the carcinogenic effects of butadiene and not an appropriate model for human risk assessment. Most notable is the mouse's relative inability to detoxify putative mutagenic/carcinogenic metabolites via epoxide hydrolase. The rat provides a better model, because of greater similarities in butadiene metabolism. If OEHHA continues to rely on the mouse data, it should acknowledge that this choice is not based on the data's quality or reliability. Rather, it is based on generic quantitative risk assessment guidelines that dictate a preference for the most sensitive species. In the case of butadiene, the weight of the available evidence demonstrates that the most sensitive species is not the best model for human risk assessment (CMA, pp. i, 3-5).

Response: Although some evidence may favor the rat model over the mouse model, the total mass of available evidence is limited. Public health protection requires consideration of all valid models, and use of health protective models unless data clearly and convincingly indicate they are not valid predictors of human toxicity. Such data are not currently available. The available BD-related data from mice, rats and primates do not clearly indicate that the rat data should be used instead of the mouse data for human cancer risk assessment. Indeed, the commenter's own demonstration of consistency between upper-bound rat-based risk projections and observations in a worker cohort provides some evidence that rat-based risk assessment may underestimate human risks and thus might not be prudent (see CMA, Appendix II, pp. 2, 5). The comment is correct in noting that in this case OEHHA staff have not moved away from the default practice of using the most sensitive site, sex, and species for human health risk assessment.

OEHHA staff believe that the mouse data are clearly superior to the rat data. The fact that the findings in mice have been replicated, whereas the findings in rats have not, is relevant. The fact that the mouse data are more detailed than the rat data is also relevant. It is more prudent to rely on detailed, replicated findings than to rely on less detailed, unreplicated findings. The availability of new data consistent with earlier findings reduces the probability that risk estimates are too low due to chance or extraneous factors.

13. Comment: The use of body surface area scaling is not appropriate for butadiene risk assessment. Such scaling implies that the rat would be more sensitive to BD on a mg/kg basis than the mouse. The mouse and rat bioassays, and OEHHA's mouse- and rat-based potency slopes, clearly show that this is not the case (and that body surface scaling is not valid). Such scaling also implies that man would be more sensitive to BD on a mg/kg basis than the mouse. The clear evidence, including both metabolism and direct tumor data, is that the mouse is the most sensitive species. "Routine" scaling is inappropriate when compound-specific information is available; several technical papers have concluded that the use of compound-specific data is preferred. For some chemicals, scaling based on mg intake/kg/day is more accurate. Surface area scaling is inconsistent with the substantial body of data on BD, including metabolism data from mice, rats, monkeys and humans. Scaling based on the 3/4 power of body weight might be used after adjusting for species differences in formation and deactivation of the "direct acting" toxicants, epoxide metabolites of BD (CMA, pp. i, 5-6).

Response: Guidelines for chemical carcinogen risk assessment (such as those cited in the response to CMA comment 11, above) generally suggest the use of a "surface area" scaling factor, in the absence of substance-specific data, largely due to empirical observations. Data from the most sensitive species are generally scaled using such a factor (usually body weight [bw] raised to the 2/3 or 3/4 power; actual surface area is commonly assumed to be proportional to bw raised to the 2/3 power). These factors are thought to represent pharmacodynamic differences among species, as well as differences in metabolic rates (for which body surface area has been thought to be a proxy -- due to heat loss). Pharmacodynamic differences involve differing responses to similar concentrations of a toxicant in tissue of different species or subgroups within species. The number of cells in a tissue, the rapidity of a tissue's growth or maturation, and the passage of a cell line through divisions towards senescence all can affect a tissue's response to a toxicant and add uncertainty to risk assessment. Thus, "surface area" (bw to the 2/3 or 3/4 power) scaling factors are used largely as uncertainty factors. Here, the surface area scaling increases the potency estimate by approximately 2-fold, so it has little impact on the overall risk estimates.

It is not certain that the B6C3F1 mouse is more sensitive than all humans (or all rats). The report of human metabolism data cited by the commenter is limited: it refers to microsomes from only 12 liver samples and 6 lung samples (the latter from surgery patients). Although the report presents Vmax values for activating (BD to BMO) and presumed detoxicating (from BMO to 1,2-dihydroxy-but-3-ene rather than DEB) transformations, it does not present the corresponding Km values which might tell us more about

the rate of these steps at low doses of BD. Moreover, the relevance of these data to carcinogenesis is unclear because we do not know with certainty which metabolites are responsible for tumor induction or promotion. Even if we knew that specific epoxides were responsible, there are insufficient data on concentrations of epoxides in target tissues to predict these concentrations in humans exposed to ambient levels of BD. Even within species, different strains or subgroups may have markedly different metabolisms. The varying susceptibility of different groups of humans to different lymphopoietic cancers (see CMA comment 5, above) may be due to differing rates of metabolism of substances like BD. Thus OEHHA staff do not believe that the data should be adjusted as suggested by the comment prior to applying a scaling factor (bw to the 2/3 or 3/4 power) in the risk assessment.

Although quite a bit of data on BD metabolism is available, it does not provide sufficient pharmacokinetic and pharmacodynamic information for OEHHA staff to adjust the (default or "routine") surface area scaling. The fact that BD appeared less potent in the rat study than in mice does not invalidate the default approach: as noted above, this approach is generally used with data from the most sensitive species, which is not always the largest. Although the mouse data, used with a scaling factor, would poorly predict responses in rats, this does not mean that the mouse necessarily poorly predicts the human response to BD. OEHHA staff have analyzed datasets used in the references cited by the commenter as supporting scaling based on bw to the 3/4 power, and found them to be consistent with 2/3 power as well as 3/4 power scaling. The data used in the report prepared by Clement Associates that suggests mg intake/kg bw/day scaling are also consistent with bw to the 2/3 power scaling. In view of the uncertainties involved with interspecies scaling, and the consistency of empirical data with 2/3 power scaling, OEHHA staff have chosen to use default scaling for the butadiene risk assessment.

It is also important to note that since surface area scaling reflects our Office's standard approach, other risk assessments developed from animal estimates for the Toxic Air Contaminants Program have used this procedure. To compare the risk from butadiene to the risk from other compounds, it is best to use similar approaches.

14. Comment: OEHHA should use the internal concentration of butadiene monoepoxide (BMO) as the measure of dose. In all butadiene risk assessment documents, BD's reactive epoxide metabolites are the putative mutagenic and carcinogenic species. BMO is the first metabolic product of BD. Thus, any pharmacokinetic model using BMO would be superior to one based on external air or absorbed levels of BD. The fact that a full physiologic model that includes diepoxybutane (DEB) or other epoxide metabolites has not yet been developed does not justify OEHHA's preference for BD over BMO. Evidence suggests that the mouse is unusual in its ability to produce DEB.

OEHHA's concerns regarding the adequacy of the available metabolism data reflect unreasonable expectations. The lack of perfect data should not be used as a justification for disregarding the enormous body of evidence which weighs in favor of using BMO as the measure of dose. OEHHA's point concerning alleged similarities between the mouse and monkey data of Dahl et al. (1990) is unfounded because it is based on

inappropriate scaling techniques. OEHHA should recognize that when adjustments for metabolism are made, the risk estimates based on the mouse and rat tumor data become reasonably consistent. This suggests that use of the metabolized dose reduces uncertainties in the risk estimates (CMA, pp. i-ii, 6-8).

Response: As OEHHA staff have noted previously (see Part C, pp. OEHHA C-4 and OEHHA C-7 to OEHHA C-8, CMA comments 6 and 15), a number of possible dose measures were considered and the continuous internal dose, based on the uptake data of Bond et al. (1986), was judged the most reliable. The available metabolic data show little or no correlation between tissue concentrations of epoxide metabolites and observed incidence of carcinogenic lesions. The production of tumors in multiple organs and lack of correlation with tissue metabolite residues suggests the use of a dose measure that is applicable to the whole animal. The relative distribution of metabolites does not explain either the lower sensitivity of rats to butadiene or the different sites of carcinogenicity in the two species. For example, the estimates and measurements for mammary tissue are not much different between the two species and the difference in response between the two species is not easily explained on the basis of metabolite levels. In view of these facts, a whole body (continuous internal) dose is the most appropriate for low dose extrapolation.

OEHHA staff are aware of the unreasonableness of expecting perfect data. Nevertheless, the lack of human metabolic data on butadiene prevents the application of the metabolic information in a reliable manner. In view of the current state of knowledge of tumor incidences and BD metabolite concentrations, OEHHA staff believe that continuous internal dose is the most reliable measure. OEHHA staff have used metabolic data in risk assessments for many compounds including methylene chloride, vinyl chloride, chloroform, trichloroethylene, perchloroethlyene and formaldehyde.

OEHHA staff found similarity between the mouse (rather than the rat) and the monkey using a common "surface area" (body weight raised to the 2/3 power) adjustment of BD uptake data. Staff do not believe this is an inappropriate technique.

OEHHA staff have addressed the adjustments for metabolism suggested by the commenter in Part C (see pp. OEHHA C-2 to OEHHA C-12, esp. CMA comments 5, 6, 17 and 21). These adjustments are based on data regarding blood epoxide levels. The epoxides referred to are not necessarily the only metabolites associated with carcinogenicity. There is no apparent correlation between tissue epoxide concentrations and tumorigenic response. Given the available data, the whole body continuous internal dose measure used in the TSD is still the most appropriate measure for low dose extrapolation. OEHHA staff declined to use the suggested adjustments in the TSD's ultimate risk assessment, and need not acknowledge properties of risk estimates based on those adjustments. OEHHA staff do recognize, however, that adjustments to the data (such as those suggested by the commenter) can allow similar risk estimates to be derived from studies in different species. It should be noted, again, that the adjustments suggested by the commenter are not based on human data.

15. Comment: The TSD should at least use the available metabolism data qualitatively. The document should acknowledge that the "best estimate" of likely excess cancer deaths from exposure to BD in ambient air is an upper bound based on conservative assumptions not specific to butadiene. The document should also acknowledge that the data indicate that the B6C3F1 mouse is uniquely susceptible to the carcinogenic effects of butadiene, and that the document's risk assessment may therefore overstate human cancer risks by a substantial margin. This should be stated wherever the document presents its "best estimate" of human cancer risks, and at the end of the fourth paragraph on p. 7 of the Executive Summary. The document should recognize that the estimate presented there is intended to be a conservative upper bound estimate of possible excess human cancer deaths, that the "best estimate" of potency is not necessarily the most plausible and is inconsistent with data from epidemiologic studies, and that the number of excess human cancer deaths from exposure to BD in California's ambient air may actually be zero (CMA, pp. ii, 8-9).

Response: The TSD generally makes clear that the "best estimate" of risk is an upper bound value. The reader can easily discern that many of the assumptions used are health conservative and not specific to butadiene. It is not clear that B6C3F1 mice is uniquely susceptible to the carcinogenic effects of butadiene, although it is apparent that they are more sensitive than Sprague-Dawley rats. Part B's summary makes it clear that the calculations presented there relate to upper bound plausible excess cancer risks and that "the actual risk, which cannot be calculated, may be much lower" (p. 1-4). In response to comments, OEHHA staff have recommended changes to the Executive Summary to note the upper bound nature of the population cancer burden estimate and the fact that actual risk may be significantly lower. However, with 30 million people in California, it is extremely unlikely that the number of excess human cancer deaths from exposure to BD in the ambient air will actually be zero. The consistency of the "best" potency estimate with the epidemiologic data is addressed in responses to several of the comments above, as well as in Section 5.3 of the TSD's Part B. OEHHA staff have compiled additional relevant information for inclusion in the TSD before the document is formally presented to the Air Resources Board.

Comments from the General Motors Corporation (GM)

1. Comment: The document still does not put the risk from butadiene concentrations into the proper perspective. It should better portray the limitations and uncertainty associated with the range of unit risk factors developed for 1,3-butadiene. Although some important caveats are present in the Part B Summary, the Executive Summary still contains an objectionable statement that can be taken out of context (at the end of the fourth paragraph on p. 7). The words "upper limit" should be included in each reference to risk. (GM comments, December 6, 1991, p. 1).

Response: The draft TSD Part B addresses specific limitations and uncertainties of the chosen risk assessment approach, in Section 4. As noted by the commenter, Part B's Summary conveys the uncertainty associated with the range of unit risk factors. OEHHA staff have recommended changes

to the TSD's overall Executive Summary to better convey this uncertainty and modify the statement found objectionable by the commenter.

2. Comment: This commenter is concerned that there is such a wide range (nearly two orders of magnitude) in the upper limit risk based on different animal models. This means that there is great uncertainty in judging the need for, and the cost-effectiveness of, any additional measures to reduce the risk. It is, therefore, extremely important to establish which animal model most closely approximates the risk to humans. A better understanding of the mechanism(s) of BD carcinogenicity is thus of paramount importance. The reader of the Executive Summary should be clearly informed of the wide range in upper limit risk, and the reasons for it (GM, pp. 1-2).

Response: As noted in the document, the range in upper limit risk estimates is based on upper confidence limits from various dose modeling approaches as well as different animal models. The TSD's Executive Summary need not detail all the reasons for this range. The Executive Summary notes that carcinogenic effects of butadiene were observed in studies of rodents. The reader can refer to Part B of the TSD for details of these studies and the risk assessment. Reasons for selecting a mouse-based risk estimate as the "best" value are also discussed there (see also the response to CMA comment 12, above). Unfortunately, insufficient data are available to clearly establish with which animal model can be used to most closely approximate the risk to humans.

Table 5-1b. Comparison of Upper-Bounds on Cancer Risk Determined from Statistically Significant Cancers among Butadiene Exposed Workers and from Potency Values Derived from Mouse Data

Study	Cohort	Assumed Butadiene Conc. (ppm)	Sample Size	Cancer Type	Observed	SMR(a) (95% UCL)	Expected	Excess Cancer Cases(b)	Upper-Bound Observed (c)	Upper-Bound Predicted (d)
Matanoski et al. (1990)	Black production workers	10	371	All cancers	19	179	16.5	11.1	30	28 (e)
		1						1.1	30	18
		10	371	All Lymphopoietic cancers	6	1107	1.2	11.1	13	12
		1						1.1	13	2
Divine (1990)	Routinely exposed workers	10	705	All cancers	42	123	46.3	3.8	57	50 - 80 (f)
		1						0.4	57	47 - 50
		10	705	Lymphosarcoma & reticulosarcoma	5	1310	0.9	3.8	12	5 - 40
		1						0.4	12	1 - 5

a. Upper-bound Standardized Mortality Ratio determined as upper-bound on observed divided by expected cases (expressed as percent)
b. Estimated from potency value derived from mouse data, with excess cancer cases estimated as unit cancer risk x butadiene concentration x 40 hr/wk x 50 wks/yr x latency correction x sample size)
c. The upper-bound on cases consistent with the epidemiological studies examined was estimated as SMR (95% upper confidence limit) x expected cases
d. Upper-bound on human cancer cases predicted as the sum of butadiene-caused cancers and the background cancer incidence.
e. Using correction for less than lifetime exposure and observation estimated from an assumed 10 out of 70 year exposure and overall mortality (deaths from all causes divided by sample size).
f. Using correction for less than lifetime exposure and observation estimated for 12.4 yrs exposure beginning at age 27.5 yrs with 30.4 yrs of followup, using Doll-Armitage multistage model with 4 to 7 stages (Brown and Chu, 1983).

STATE OF CALIFORNIA
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PETE WILSON, Governor

December 8, 1991

Dr. James W. Pitts, Chair
Scientific Review Panel
Air Resources Board
P. O. Box 669
San Clemente, CA 92674-669

Re: Risk Evaluation

Dear Jim,

I have become increasingly more concerned over the manner in which risk numbers are being used and possibly misused by the Districts and would like help from you and the Scientific Review Panel in better presenting the significance of the risk evaluation process.

As you know, the Tanner process requires a risk evaluation to be made by DHS (now OEHHA) in the identification and assessment of possible toxic air contaminants. The assumptions, extrapolations, limited experimental data, inferences and contradictory reports in making a determination are many but do not prevent us from reaching a decision, usually made very conservatively, as to whether or not a substance is a toxic air contaminant.

Our decisions are often troubling because the data are limited. However, if a data on a compound are such that it may cause cancer we identify it as a TAC. We have no difficulty in accepting this process.

What is becoming apparent is that the unit risk values developed in the identification of air toxics are now being proposed as regulatory or control values. This concept I do have difficulty with and would like your input.

For the 15 compounds we had considered up through perchlorethylene our risk management (regulatory) actions have involved using BACT control technology, phasing out, prohibition, or the promotion of substitute compounds. This process has worked fairly well.

It seems to me, to now use risk values prepared for identification and assessment of TACs for risk management purposes is not only inconsistent with what we have done to date but also misuses the information gathered for the risk assessment process.

Specific questions I have include:

Should we be using risk assessment numbers for risk management (control)?

Under what conditions, if any, should risk assessment numbers be considered for control?

How can the Board and the public be better informed of the limitations and usefulness of the risk assessment process?

Do you believe a separate and independent risk evaluation process is appropriate for the regulatory control process?

What are the limits of the risk assessment evaluation process?

What does a "best value" for cancer mean? Is it for identification and possible rating of a compound?

Some Districts would like to identify a "bright line" for risk management. That is a specific risk number, above which no permits would be given and below which permits would be allowed. This absolute level is proposed to be tied to the risk assessment best value level. I do not believe that is our intent. That is the reason I am hoping that you and the Scientific Review Panel can give us some help.

It would also be helpful to give us some of the considerations being made by the National Research Council study on Risk Assessment of Hazardous Air Pollutants even before its expected report due in May 1993.

Jim, I would be pleased to discuss these concerns with you at your convenience. You can reach me at (510) 376-7288.

I will look forward to your input.

Sincerely,

John S. Lagarias
Board Member

cc: J. Sharpless
SRP Members

State of California

MEMORANDUM

To : Scientific Review Panel Members

Date : January 16, 1992

Subject : 1,3-Butadiene

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
From : Air Resources Board

Enclosed are copies of the public comment letters received on the SRP version of the 1,3-butadiene identification report, and the ARB staff's written responses to the exposure assessment-related comments. The OEHHA staff are in the process of drafting their responses to the health risk assessment-related comments received, and will be providing these to you at the SRP's January 23, 1992, meeting in Burlingame. These materials will be discussed during the meeting.

If you have any questions, I can be reached at (916) 322-7072.

cc: William Lockett
Bruce Oulrey
Dr. James N. Pitts, Jr., Chairman/SRP

Enclosure

DRAFT

Air Resources Board Staff Responses to Summarized Comments on the SRP Version Draft Part A and the Executive Summary

- Chemical Manufacturers Association (CMA), December 6, 1991.

Comment: The ARB staff only provided a 30-day period for submission of comments on the SRP Version of the draft report. This was not sufficient time for preparation of comprehensive comments on the new risk assessment. We recommend that whenever a new risk assessment is presented, the ARB staff provide at least 60 days for comment.

Response: The public and industry have been given a number of opportunities to comment on the proposed identification of 1,3 butadiene as a toxic air contaminant. The initial public request for information was made in January, 1988. 1,3 butadiene was entered into the identification process in Septmeber 1988. Based on information from the scientific literature and the public request, the ARB and OEHHA staffs prepared an initial draft of the 1,3 butadiene report. This report was released to the public in January, 1991 for a 30-day review period. In March, 1991 the ARB and OEHHA staff conducted a public workshop on the document. Based on the comments received during the first comment period and the workshop, the report was revised and the best value was lowered. In November, 1991 the report was re-issued for another 30-day comment period and was submitted to the SRP on January 3, 1992. If the SRP finds the 1,3 butadiene report acceptable, the final version of the report will be issued for a 45-day public comment period before the Board hearing.

- **General Motors (GM)**, December 6, 1991

Comment 1: The SRP Version of the draft report does not properly inform the reader that the risk from motor vehicle 1,3-butadiene emissions has been reduced dramatically over the past 20 years and will continue to decrease substantially over the next 20 years from fuel and vehicle regulations already on the books. While the text correctly states that 1,3-butadiene emissions are expected to steadily decrease through 2010 with the current regulations. It would be useful to provide a quantitative estimate of the decrease to put the risk for past, current and future exposures in perspective.

Response: California's toxic air contaminant program, as mandated by Health and Safety Code Section 39650 et seq., requires that the ARB identify and control substances that "may pose a present or potential hazard to human health." The purpose of the substance evaluation by staff of the ARB and OEHHA during the identification phase is to determine present exposure and risk. Furthermore, a quantitative estimate of future exposures cannot accurately be made because of the number of variables involved. For example, information obtained through the US EPA's SARA 313 program indicate that 1,3-butadiene usage in 1991 has increased by 55 percent over 1990 usage. That increase may or may not result in increased emissions to the atmosphere, and staff do not

know if the usage increase will continue. Additionally, economic factors are having an impact on the replacement of older vehicles (that emit more 1,3-butadiene than newer vehicles) in California's passenger vehicle fleet.

Comment 2: Evidence that current ambient 1,3-butadiene concentrations are only a fraction of the ambient concentrations that existed 20 years ago should be included in Part A and the Executive Summary. The continued reductions should be quantified and summarized in the documents, in particular those resulting from the 26 to 29 percent reductions in emissions from gasoline-powered motor vehicles anticipated when Phase 2 gasoline is introduced.

Response: As discussed in the response to comment 1, the focus of the "identification report" is on present risk. Presently, California's air is being impacted by non-Phase 2 gasoline combustion products. Future motor vehicle emissions of 1,3-butadiene are expected to be reduced per vehicle as a result of Phase 2 gasoline usage, however, there will continue to be additional vehicles introduced to California as the population increases.

Comment 3: The Executive Summary question "are emissions of 1,3-butadiene expected to increase in the state?" should be restated as "what are past, current, and expected future emissions of 1,3-butadiene?." The answer to the new question should document the significant emission reductions that have occurred over the past 20 years, and are expected over the next 20 years. Staff responses to the earlier GM comments on this issue should be part of the Executive Summary, not relegated to page 573 of Part C.

Response: Please see staff responses to comments 1 and 2.

Comment 4: GM recommends that information on the formation of 1,3-butadiene be included in Part A, including the chemical mechanisms involved and the experimental Auto/Oil Air Quality Improvement Program findings that have identified the effects of changing fuel variables. An understanding of the mechanisms of 1,3-butadiene formation may lead to further fuel composition changes that materially reduce 1,3-butadiene.

Response: Information on the formation of 1,3-butadiene during combustion of petroleum fuels will be added to the Board Version of Part A. The experimental Auto/Oil data has not been added to Part A, however, that data will be used by staff during the risk management phase if 1,3-butadiene is identified by the Board as a toxic air contaminant.

Comment 5: The draft report states that 1,3-butadiene may be released to the environment as tires wear, but indicates that there is not enough information to support or deny the theory. Cadle and Williams have

positively identified 1,3-butadiene and five other monomers and dimers of styrene-butadiene rubber copolymers as gaseous emissions from tire wear. Although the emission rate for 1,3-butadiene/isoprene was below 0.1 mg/km/tire in average wear conditions, this small emission should not be neglected.

Response: Based on the information found in Cadle and Williams' study of automobile tire emissions (S. H. Cadle and R. L. Williams, Gas and Particle Emissions from Automobile Tires in Laboratory and Field Studies, J. Air Pollut. Control Assoc., 28, 502, 1978.), the Part A will be revised to state that 1,3-butadiene is emitted to the environment as tires wear. A statewide emission estimate for 1,3-butadiene from tires has not been developed for the Part A since 1,3-butadiene and isoprene emissions were quantified together in the laboratory study. The staff of the ARB will continue to investigate tires as a source of 1,3-butadiene emissions.

Comment 6: The US EPA's Science Advisory Board has recently recommended that the US EPA target its environmental protection efforts on the basis of opportunities for the greatest risk reduction. The US EPA were told that they should weigh the relative risks posed by different environmental problems, determine if there are cost-effective ways to deal with the problems, and then identify the most cost-effective risk reduction options. Additionally, risk rankings should be based on total human exposure to specific toxic agents.

Response: Staff has previously responded to this comment in Part C, page 569, paragraphs 2 and 3. The response: "The 1990 Amendments to the Clean Air Act list 189 substances (e.g., 1,3-butadiene) as hazardous air pollutants (HAPs), all of which must be evaluated by the US EPA in a risk management program. It was in this context that the SAB advised the US EPA to target their risk management efforts towards the substances (HAPs) that represent the greatest public risk.

California's risk assessment/risk management program is (by law) separate and distinct. First, substances are evaluated in an "identification" phase where it is demonstrated that there is public exposure to a substance which results in an increased public risk. The second step is the "control" phase where risk reduction measures are developed for the identified toxic air contaminants (TACs). California law (California Health and Safety Code Section 39655) requires the ARB to identify all HAPs as TACs." During the control phase, similar to the US EPA, individual and multi-compound risks are assessed, and corresponding cost-effective reduction options are considered.

Comment 7: As the ARB enters the risk management phase of its consideration of 1,3-butadiene and other airborne toxics, GM recommends that decisions be made based on improved risk assessment methodologies rather than on theoretical upper limits for unrealistic exposure scenarios.

Response: Staffs of the ARB and the OEHHA use the risk assessment methodology outlined in the Guidelines for Chemical Carcinogens: Risk Assessment and Their Scientific Rationale, 1985. While staff endeavor to improve the risk assessment methodologies, the California Health and Safety Code (Section 39650e) states that "while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health."

The focus of the risk management phase is directed toward control of emissions from particular types of sources. Exposure scenarios are based on measured variables such as flow and usage rates, stack parameters, emission factors, and impacted population.

Comment 8: GM urges the ARB to participate in and coordinate its efforts with the federal efforts to improve, harmonize, and reduce the uncertainty in risk assessment. For example, the US EPA is carrying out a study and workshop on the need to control mobile-source related toxics, including 1,3-butadiene. Also, the Office of Science and Technology Policy's 1985 Document on Carcinogenicity will be reviewed by a number of federal agencies as part of an effort to coordinate risk assessment practices.

Response: The risk assessment/risk management process used by the staffs of the ARB, the local air pollution control districts, and the OEHHA is the result of Californian state law (AB 1807 Assemblywoman Tanner, 1983). Also this California process is presently under review to assess options for dealing with the uncertainties. Public workshops will be held to develop future guidelines and policy. Federal guidelines and policies are included in any state review of California's risk policies. Furthermore, the staff of the ARB and OEHHA regularly work with the US EPA during the development of risk control strategies and risk assessments, and will continue to do so.

Comment 9: In previous comments GM recommended that data from the Auto/Oil Air Quality Improvement Program (AQIRP) be used to provide a better basis for statistically robust mobile source inventories. Instead, ARB staff used unpublished data to estimate that 1,3-butadiene emissions from catalyst equipped vehicles are 0.59 weight percent of total organic gas (TOG) emissions. The AQIRP data demonstrates that 1,3-butadiene is a smaller percentage of TOG (0.38 for 1989 catalyst equipped vehicles and 0.34 for 1983-1985 catalyst equipped vehicles) than the ARB data indicate. The massive additional data on reformulated gasoline also suggest that 1,3-butadiene is between 0.3 and 0.4 percent of TOG, adding substantial credence to the use of the AQIRP data.

Response: The data (available to the public) used by the ARB staff to develop 1,3-butadiene emission estimates for catalyst-equipped light-duty passenger vehicles was derived from ARB emissions testing of 62 in-use passenger vehicles taken (with the exception of 1 vehicle) from the Light-duty Vehicle Surveillance Program. The vehicles were emissions tested in "as-received" condition (no tune-ups, tune-downs, or fuel

changes), and were selected to represent, as near as possible, the on-road vehicle population. The emission factor is a composite of the mean value of all of the tested vehicles. Although the AQIRP data and emission estimates are based on fewer vehicles and "industry average" gasoline, the results of the analysis are interesting and useful for comparison with the ARB data. The AQIRP information has been used by ARB staff in the development of the Phase 2 reformulated gasoline regulatory package to estimate reductions in the per-vehicle emissions of 1,3-butadiene when Phase 2 gasoline is sold statewide in 1996.

Comment 10: The staff response to GM's earlier recommendation to use the AQIRP data neglects to mention the industry average gasoline data and indicates that the gasolines used in AQIRP are prototype. The ARB's recent Phase 2 gasoline regulatory package used the AQIRP data to estimate that a 26 to 29 percent reduction in 1,3-butadiene emissions will be associated with Phase 2 gasoline. Thus, Phase 2 gasoline (because it will be introduced throughout the state and used throughout the vehicle fleet) will substantially reduce statewide 1,3-butadiene emissions.

Response: The AQIRP emission factors are based on "industry average" fuel (a fuel that contains the average fuel components, in average concentrations, for gasoline sold in the United States) and "reformulated" fuel. The ARB's Phase 2 gasoline regulatory package used AQIRP data to estimate a 26 to 29 percent reduction in 1,3-butadiene emissions for vehicles using Phase 2 gasoline rather than "California average" gasoline. Refineries are not required to sell Phase 2 gasoline to gas stations until March 1996. One of the goals of the Phase 2 gasoline program is the reduction of 1,3-butadiene emissions from motor vehicles.

Comment 11: GM continues to believe that the individual organic species data from the South Coast Air Quality Study (SCAQS) should be analyzed in terms of spatial and temporal variability to provide input for more refined exposure analysis. In order to properly account for the population exposure to 1,3-butadiene, spatial and temporal differences in ambient concentrations as well as indoor concentrations will need to be taken into account.

Response: The ARB staff are analyzing the individual organic species data from the SCAQS to learn more about the pollution dynamics of the South Coast Air Basin. While much of the pollution dynamics information from the SCAQS can be applied to other areas of California, the concentrations data derived from the SCAQS is South Coast-specific and cannot be used to represent conditions in California's other 13 air basins.

The 1,3-butadiene concentrations data derived from the ARB's toxic monitoring network have been used to develop air basin and statewide exposure averages for outdoor air. The use of "average" outdoor

concentrations reduces the numbers of opportunities to over- or under-estimate the actual exposure (and associated risk). Indoor exposures are considered separately. The ARB is concerned about indoor air pollution and regularly sponsors indoor air exposure research, however, the ARB does not presently have control authority over indoor air.

Comment 12: GM recommends that early-morning SCAQS 1,3-butadiene/TOG ratios be analyzed to shed light on the ARB's estimated inventory.

Response: The on-going analysis of the SCAQS data includes the analysis of 1,3-butadiene/TOG ratios. The SCAQS data represents "episode" conditions in the South Coast Air Basin, while the ARB's emissions inventory seeks to estimate average emissions.

The ARB's motor vehicle inventory has recently (1991) been updated as a result of 1,3-butadiene emissions testing for on-road motor vehicles by the ARB's Mobile Source Division. The revised emission estimates for motor vehicles have been reported in the SRP version Part A.

Comment 13: GM is concerned that ambient exposures from urban monitoring is used to characterize the total population of California. A portion of the population resides in more rural locations where the 1,3-butadiene concentrations are expected to be below typical urban levels. If this is taken into account, the statewide average ambient exposure and accompanying risk would be reduced somewhat.

Response: The toxic monitoring network primarily represents urban exposures, which is appropriate since California is a heavily urbanized state. Analysis of concentrations data from the ARB's toxic monitoring network indicate that 1,3-butadiene concentrations and emissions are higher in urban areas. Rural populations included in the statewide averaging may experience a lower exposure to 1,3-butadiene than the statewide population-weighted average. Conversely, people in the heavily-populated South Coast Air Basin are experiencing a higher exposure than the statewide population-weighted average. The population-weighted exposure average represents the "average" Californian's exposure, and is only an estimate of the average exposure in the State.

Comment 14: GM is concerned that the upper limit risk calculations in Part B do not provide an assessment of the actual risks that Californians experience as they are exposed to 1,3-butadiene in their daily lives. A knowledge of the relative contributions of individual sources is important for better estimates of public exposure.

Response: Staffs of the ARB and the OEHHA agree that information about the relative contributions of individual sources is important for better estimates of public exposure. It is anticipated that individual source data will become available through the AB 2588 Air Toxics "Hot Spots" Program. During the risk management phase, should 1,3-butadiene be

identified as a toxic air contaminant, these data will be further assessed.

Comment 15: A National Research Council review of human exposure assessment for airborne pollutants stated that "risk reduction strategies that address only outdoor air are only partially effective. Such strategies need to be modified to better address the importance of indoor exposures." They also indicated that all media and routes of exposure should be assessed.

Response: Staff has previously responded to this comment in Part C, page 569, paragraph 7. The response: "The ARB has been given authority to identify and control outdoor TACs. The ARB staff recognize that indoor air exposures can pose a significant risk, and staff agree that consideration of indoor air and other routes of exposure are important for a complete risk assessment. Available information on indoor air, food, and water exposure has been reported in the document. Because indoor exposures can be significant, the ARB is continuing to sponsor research to develop data on indoor air exposures to TACs."

Comment 16: The US EPA's comparison of benzene emissions versus human exposure (the TEAM study) indicates that, although motor vehicles emit 82 percent of the benzene, they are only responsible for 18 percent of the individual exposures (based on personal monitoring). The TEAM study showed how significant individual sources of exposure are because the general public spends most of its time indoors.

Response: Staff agree that the average Californian spends the majority of their time indoors, and that indoor exposures can be the most significant exposure that they receive from certain pollutants. In the case of 1,3-butadiene, indoor exposure to 1,3-butadiene from environmental tobacco smoke will probably be higher than the local outdoor concentration (in the absence of "hot spot" outdoor emission sources). As has been discussed in other responses, the ARB is concerned with indoor air pollution.

Comment 17: The report does not provide the proper perspective on the risk from motor vehicles relative to the much larger risks from indoor sources, particularly to the substantial 1,3-butadiene exposure experienced by both smokers and non-smokers from cigarette smoke and environmental tobacco smoke. In response to the Executive Summary question "what about indoor exposure to 1,3-butadiene?", the response indicates that indoor air may be the major route of exposure to individuals exposed to a heavy smoking environment. Based on available data it is clear that indoor air <u>is</u> the major route of exposure for smokers and those exposed to a heavy smoking environment, and that exposure to environmental tobacco smoke <u>is</u> a major route of exposure to 1,3-butadiene for Californians. The response to this question should also include comparisons of the average daily intake of 1,3-butadiene from smoking, typical environmental tobacco smoke exposures, heavy exposures, and exposures to ambient air.

Response: 1,3-Butadiene exposures experienced by smokers and non-smokers from cigarette smoke and environmental tobacco smoke may result in a more significant risk than the risk imposed by ambient motor vehicle-derived concentrations of 1,3-butadiene. However, available data do not lead to the unequivocal conclusion that indoor air is the major route of exposure for all Californians in a smoking environment. In the Northern California study, 34 percent of the homes were reported to have smokers present, yet only 8 percent of the total had measurable levels of 1,3-butadiene. The remaining 26 percent of the homes where smoking occurred had 1,3-butadiene concentrations below the limit of detection. The Executive Summary gives estimated inhaled doses of 1,3-butadiene for heavy smoking environments (the tavern and bar). However, broad quantitative comparisons of exposures with different levels of ETS simply cannot be made at this time due to a lack of comprehensive data.

Comment 18: Regarding indoor air concentrations of 1,3-butadiene, the statement that "it appears reasonable to assume that residential exposures ... may typically be close to ambient levels" is not supported by the data provided. The detection limit used in the Woodland study (0.54 ppb) is significantly above the statewide average ambient exposure, so no comparison of residential and ambient exposures can be made.

Response: Further research is needed using a greater number of homes sampled over different seasons with an improved detection limit before conclusions can be drawn regarding typical indoor concentrations. The referenced sentence will be changed in the Board version of the report.

Comment 19: The statement that non-smoking residential exposures may typically be close to the statewide average ambient exposure is not supported by the data provided because the limit of detection was too high. The statement should be replaced with one that acknowledges that there is not enough information to make a quantitative comparison between ambient exposures and non-smoking residential exposures.

Response: Please see the response to comment 2818.

Comment 20: GM encourages ARB to carry out a study of residences, offices, and commercial spaces using a technique that has a detection limit similar to that of the Woodland pilot study (0.05 ppb). Such measurements, in conjunction with estimates of smoking, would go a long way toward establishing the exposures and health effects of environmental tobacco smoke.

Response: We acknowledge the need for studies that would further monitor a wide variety of indoor environments for toxic air contaminants. Such studies would need to obtain activity data and ambient concentrations data as well.

Comment 21: Using the NRC reported value for the average emission rate of respirable suspended particulate matter per cigarette in sidestream smoke (26 mg), the US EPA calculated a daily intake for passive exposure of 3 mg. Using the same methodology for 1,3-butadiene (with an emission rate of 400 ug per cigarette), one can calculate the average daily intake of a passive smoker to be 46 ug. This can be compared to an average daily intake of 16.4 ug for an individual exposed for 24 hours to the average ambient concentration of 0.37 ppbv. Thus, the typical exposure from smoking exceeds that of typical outdoor concentrations. GM recommends that calculations of 1,3-butadiene exposure from smoking and from passive exposure to ETS be included in Part A and in the Executive Summary to provide perspective for the reader.

Response: Exposure calculations are based on actual measured indoor concentration estimates, not on extrapolated emissions data. Emission rates are only one of many factors that determine indoor exposures. Concentrations in an indoor environment can be decreased by ventilation (outdoor air exchange) and by reaction with other ETS constituents. As discussed in an earlier response, data from the Northern California study were inconclusive regarding the degree to which the presence of smoking affected butadiene concentrations. In that study, many of the ETS homes with butadiene concentrations below the limit of detection had as many cigarettes smoked in them as ETS homes with measureable butadiene concentrations.

CHEMICAL MANUFACTURERS ASSOCIATION

Gordon D. Strickland
Vice President-Technical Services

December 6, 1991

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: 1,3 Butadiene
P.O. Box 2815
Sacramento, California 95812

Re: The Scientific Review Panel Version of the Report to California Air Resources Board on the Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant

Dear Ms. Shiroma:

The Butadiene Panel of the Chemical Manufacturers Association is pleased to submit the enclosed comments on the Scientific Review Panel version of the report to the California Air Resources Board on the Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant. The Panel consists of the major U.S. producers and some users of butadiene.

The Panel has previously reviewed and commented on the Preliminary Draft Report for this proposal. The Panel notes with appreciation that several changes to the Report have been made in response to the earlier comments. However, the Panel continues to believe that the quantitative risk estimates contained in the Health Assessment document (Part B of the Report) overstate the potential human cancer risks by a wide margin.

Please direct any questions that you may have regarding these comments to Dr. Elizabeth J. Moran, Manager of the Butadiene Panel, at (202) 887-1182.

Sincerely,

Gordon D. Strickland

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STATE OF CALIFORNIA
AIR RESOURCES BOARD
STATIONARY SOURCE DIVISION

COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION BUTADIENE PANEL ON THE SCIENTIFIC REVIEW PANEL VERSION DRAFT REPORT ON THE PROPOSED IDENTIFICATION OF 1,3-BUTADIENE AS A TOXIC AIR CONTAMINANT

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December 6, 1991

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EXECUTIVE SUMMARY

The Butadiene Panel of the Chemical Manufacturers Association has reviewed the Scientific Review Panel (SRP) version of the draft report to the California Air Resources Board (CARB) on the Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant. This report was prepared by the staffs of CARB and the Office of Environmental Health Hazard Assessment (OEHHA). The Panel has previously reviewed and commented on the Preliminary Draft Report for this proposal. The Panel notes with appreciation that several changes to the Report have been made in response to the earlier comments. However, the Panel continues to believe that the quantitative risk estimates contained in the Health Assessment document (Part B of the Report) overstate the potential human cancer risks by a wide margin. In particular, the Panel offers the following comments and recommendations:

1. OEHHA's "best estimate" of the human potency or slope factor for butadiene of 0.37/ppm, based on lung tumors in female mice, is inconsistent with the results of butadiene epidemiology studies. This can be demonstrated by comparing the number of observed cancer deaths in various epidemiology studies with the number of deaths that would be predicted based on a potency slope of 0.37/ppm.

2. OEHHA's reasons for basing its best estimate of human cancer risks on the B6C3F1 mouse data are not valid. The available data on butadiene metabolism and mechanism of action indicate that the B6C3F1 mouse is uniquely susceptible to the carcinogenic effects of butadiene and not an appropriate model for human risk assessment. The rat provides a better model for human risk assessment.

3. The use of body surface area scaling for the quantitative risk estimates is not appropriate for butadiene. Body surface area scaling implies that the rat would be more sensitive on a mg/kg basis to butadiene than the mouse. However, the mouse and rat cancer bioassays show that this clearly is not the case for butadiene. Surface area scaling is inconsistent with the substantial body of data that has been developed on butadiene metabolism in mice, rats, monkeys and humans.

4. OEHHA should use the internal concentration of the reactive butadiene monoepoxide for the measure of dose. OEHHA's criticisms of the available data on species differences in metabolism of butadiene are overstated. These data can and should be used to

develop more realistic estimates of butadiene cancer risks for humans.

5. If CARB is unwilling to use butadiene metabolism data for its quantitative risk estimates, then CARB at least should use these data qualitatively. Specifically, CARB should acknowledge that: (i) Its "best estimate" of likely excess cancer deaths from exposure to butadiene in ambient air is an upper bound estimate based on numerous conservative assumptions that are derived from general risk assessment guidelines, rather than butadiene-specific data. (ii) The available data on butadiene metabolism and mechanism of action indicate that the B6C3F1 mouse is uniquely susceptible to the carcinogenic effects of butadiene. The quantitative risk assessment therefore may overstate human cancer risks by a substantial margin, and perhaps by several orders of magnitude. (iii) The number of excess human cancer deaths from exposure to butadiene in ambient air in California actually may be zero.

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INTRODUCTION

The Butadiene Panel of the Chemical Manufacturers Association appreciates this opportunity to comment on the Scientific Review Panel (SRP) version of the draft report to the California Air Resources Board (CARB) on the Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant. The Panel consists of the major domestic producers and some users of butadiene. A list of Panel member companies is attached as Appendix I.

The Butadiene Panel submitted comments to CARB in March 1991 on the Preliminary Draft Report on the proposal to identify butadiene as an air toxic. These earlier comments are included in Part C to the SRP version of the draft report. The Panel's current comments address the Health Assessment document prepared by the Office of Environmental Health Hazard Assessment ("OEHHA"), which is Part B of the SRP version of the draft report. This Health Assessment document contains a new quantitative risk estimate based on the second mouse bioassay sponsored by the National Toxicology Program (NTP-II).

CARB has provided only a thirty-day period for submission of comments on the SRP version of the draft report. This was not sufficient time for preparation of comprehensive comments on the new NTP-II risk assessment. (We recommend that CARB provide at least sixty days for comment whenever a new quantitative risk assessment is presented.) Accordingly, these comments address the Panel's primary reasons for believing that OEHHA's "best estimate" of butadiene cancer risk overstates by a substantial margin the likely human cancer risks from exposure to butadiene in ambient air.

At the outset, the Panel wishes to commend OEHHA for including in the Health Assessment a generally complete presentation of the toxicology literature on butadiene, including elements of relevant comparative metabolism. OEHHA also is to be commended for presenting a range of risk estimates based on mouse and rat tumor data sets. The recognition that butadiene epoxide metabolites are the putative mutagenic and carcinogenic moieties is an important component of the data set. The Butadiene Panel agrees with OEHHA's presentation of this concept in the document.

The Panel feels strongly that OEHHA should use more of these data for its "best estimate" of likely human cancer risks for butadiene. The "best estimate" of cancer risk selected by OEHHA is an upper bound estimate based on several "worst case" assumptions that are implicit in generic cancer risk assessment guidelines. The collective use of these worst case assumptions to arrive at a potency slope value of 0.37/ppm is not realistic and does not provide a reasonable basis for estimating likely excess human cancer deaths from exposure to butadiene in ambient air.

The alternative risk assessments which are included in the OEHHA health assessment document demonstrate the range of potential risk estimates which may be derived when different assumptions are applied. The available evidence on butadiene metabolism and mechanism of action provides strong support for the use of alternative data sets, such as the rat bioassay and comparative metabolism, to arrive at the best estimate of risk. The Panel believes use of the complete data set would produce more plausible and scientifically supportable estimates of human cancer risks.

Many of these issues were addressed at length in the Panel's earlier comments. The Panel also addressed many of these butadiene risk assessment issues in documents recently submitted to OSHA in connection with ongoing rulemaking proceedings regarding occupational exposures to butadiene. These documents include statements by Stuart Z. Cagen, Ph.D., of Shell Oil Company, and Thomas B. Starr, Ph.D., of Environ Corporation, in response to a NIOSH quantitative risk assessment based on the second NTP mouse study, and a statement by Michael G. Bird, Ph.D., of Exxon Biomedical Services, Inc., that summarizes the most recent butadiene metabolism data. Copies of these materials are included as appendices to these comments. These statements provide additional support for the points presented in these comments.

I. THE "BEST VALUE" POTENCY SLOPE OF 0.37/PPM IS NOT CONSISTENT WITH THE AVAILABLE EPIDEMIOLOGY DATA.

One way to assess the plausibility of OEHHA's "best estimate" of human cancer risks is to compare the observed cancer rates in epidemiology studies of butadiene-exposed workers with the number of cancer deaths that would be predicted from OEHHA's "best estimate." Such a comparison has been performed by Thomas B. Starr, Ph.D., of Environ Corporation. See Environ (1991a) (attached as Appendix II). Dr. Starr's analysis shows that the observed cancer rates in epidemiology studies on butadiene-exposed workers are not consistent with the cancer rate which is predicted using the 0.37/ppm potency slope.

Indeed, Dr. Starr's analysis shows that the probability of OEHHA's "best estimate" being correct is infinitesimally small -- 6.9×10^{-44} -- based on all cancers and assuming the production workers used in Dr. Starr's analysis were exposed to 10 ppm butadiene. While this exposure assumption seems reasonable (Environ 1991, Acquavella 1991), even if one assumes average workplace exposure levels were only 2 or 1 ppm, Dr. Starr's analysis still shows that OEHHA's "best estimate" is highly improbable (probabilities are 3.8×10^{-17} and 1.0×10^{-5} for 2 and 1 ppm, respectively). Similar results were obtained in a consistency check performed by Acquavella (1991) (addressing the NIOSH NTP-II risk assessment -- see Part 3 of Appendix III attached hereto).

OEHHA also has performed a consistency check of its quantitative risk assessment. However, this consistency check is based only on the maximum likelihood and upper bound potency estimates (0.0168 and 0.089 per ppm, respectively) derived from the incidence of malignant lymphomas in male mice in NTP-I. No justification is presented for excluding entirely OEHHA's "best estimate" of 0.37/ppm from the consistency check.

It also should be noted that, whereas OEHHA's "best estimate" is based on lung tumors in female mice, none of the epidemiology data suggest that the lung is a target organ in humans. Indeed, in every butadiene epidemiology study conducted thus far, a deficit in lung tumors has been observed. Acquavella (1990, 1991). This fact should be acknowledged in OEHHA's discussion of the epidemiology studies.

Additionally, the Panel believes OEHHA's analysis and interpretation of the butadiene epidemiology studies (pages 3-20 to 3-28) are flawed in several critical respects. These points are addressed at length in Appendix IV to these comments, which is devoted exclusively to epidemiology issues. Acquavella (1991a).

II. OEHHA'S REASONS FOR PREFERRING THE MOUSE DATA OVER THE RAT DATA FOR THE "BEST ESTIMATE" OF HUMAN CANCER RISKS ARE NOT VALID.

OEHHA cites several reasons for preferring the mouse data for its "best estimate" of excess cancer risk. These pertain largely to the fact that the mouse study was repeated at lower doses and obtained consistent results, and reportedly the mouse data are available in greater detail, allowing more in-depth analysis, compared to the rat data. See p. 4-24. These asserted justifications do not provide a valid basis for preferring the mouse data over the rat data for the best estimate of human cancer risks. Similar arguments have been advanced by NIOSH, and these arguments are addressed in Cagen (1991) (attached as Appendix V).[1/]

1/ OEHHA also cites "suggestions from limited epidemiological observations that butadiene exposure may be associated in humans with lymphatic and hematopoietic cancers" as a reason for choosing the mouse data for its best estimate of risk. See pp. 4-27. The epidemiology data do not provide any basis for preferring the mouse data over the rat data. In addition to the Panel's disagreements with OEHHA's evaluation of the epidemiology studies (see Acquavella (1991a) attached as Appendix IV), the increased incidence of lymphocytic and hematopoietic cancers in B6C3F1 mice has been observed only at relatively high doses and may well reflect the presence of an endogenous retrovirus present in the B6C3F1 mouse but not in humans. See Bird (1990). The

A more thoughtful and objective approach would be to acknowledge that all three cancer bioassays are valid and adequate for quantitative risk assessment, although the results seen in the two species tested differ dramatically. The objective for the risk assessor, then, is to choose the species which provides the best model for human risk assessment. The Butadiene Panel believes that the rat provides the better model because of greater similarities between the rat and human in the metabolism of butadiene, and because of the demonstrated unique susceptibility of the B6C3F1 mouse to butadiene-induced toxicity. See the Panel's March, 1991 comments, at pp. 18-21.

The available metabolism data, including human in vitro data, demonstrate clearly that the mouse produces more active epoxide metabolite(s) and detoxifies these metabolites less efficiently than rats, monkeys, and humans. Thus, there is a greater tendency for toxic butadiene metabolites to accumulate in mouse tissues. See Bird, 1990 (submitted with earlier Panel comments); Bird, 1991 (Appendix VI); Cagen, 1991 (Appendix V); Environ, 1991 (Appendix VII). Most notable is the mouse's relative inability to detoxify the metabolites via epoxide hydrolase with the resultant accumulation of putative mutagenic/carcinogenic metabolites. This is evident from the observed differences in urinary metabolites (Henderson et al. 1991), the interspecies differences in metabolism (Csanady and Bond 1991), and subsequent blood levels of circulating metabolites. Dahl et al. (1991). The collective evidence demonstrates clearly that the mouse is at an unusual disadvantage because of its propensity to accumulate higher levels of butadiene reactive metabolites, compared to rats, monkeys, and humans. Cagen (1991).

In addition, the evidence clearly demonstrates that the mouse is more susceptible than other species, including primates, to the bone marrow toxicity of butadiene. Butadiene effects bone marrow stem cell development and induces cytotoxicity in the mouse. Liederman et al. (1986); Irons et al. (1986). Such bone marrow toxicity has not been seen in the rat (Owen et al. 1987; Cunningham et al. 1986), the primate (NTP 1989), or man. Checkoway and Williams (1982). See Acquavella (1991a) in Appendix IV for additional discussion of the study by Checkoway and Williams.

If OEHHA continues to rely on the mouse data, it should acknowledge that this choice is not based on greater quality or reliability of the mouse data compared to the rat data. Rather, OEHHA's choice of data set is based on generic quantitative risk assessment guidelines that dictate a preference for the most

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relevance of these tumors for an assessment of potential human cancer risks from exposure to part per billion levels of butadiene in ambient air is extremely doubtful.

sensitive species. In the case of butadiene, however, the weight of the available evidence demonstrates that the most sensitive species is not the best model for human risk assessment.

III. SURFACE AREA SCALING IS NOT APPROPRIATE FOR BUTADIENE.

"Routine" scaling adjustments based on surface area are not justified when compound-specific comparative species information is available. The butadiene data set, considered as a whole, strongly indicates that interspecies scaling on a surface area basis is inappropriate.

Several papers that have studied appropriate interspecies scaling options have concluded that the use of compound specific data is preferred:

> O'Flaherty (1989) at page 597: "In the absence of specific information bearing on the metabolism and toxicity of the chemical, the 0.75 power of body weight dose conversion is a reasonable approach. . . ."
>
> Travis and White (1988) at page 124: "The National Academy of Sciences and Anderson point out that scaling should depend on the kinetic behavior of the particular compound and mechanism of toxicity . . . the 3/4 [0.75] power may be the most appropriate interspecies scaling factor for use in risk assessment of direct acting compounds. Further analysis will be needed to determine the appropriate scaling factors for compounds that are activated by metabolism."

An EPA-sponsored report prepared by Clement Associates made quantitative comparisons of carcinogenic potency in animals and humans for 23 chemicals for which suitable animal and human data were available. The study concluded that the "use of mg intake/kg body weight/day method for animal-to-human extrapolation generally causes risk related doses (RRDs) estimated from animal and human data to correspond more closely than other methods evaluated . . ." EPA (1987); see also Allen et al. (1991).

Considering what is now known about the toxicity and metabolism of butadiene in a variety of species, it is imperative to use the compound specific information to arrive at the most scientifically-based scaling factor when extrapolating to humans. For example, because it is universally accepted that epoxide metabolite(s) are the "direct acting" toxicants, scaling based on a 3/4 power of body weight might be used only after adjustments are made to account for species differences in the formation and deactivation of these toxic metabolites. Recent data of Csanady and Bond show that human tissues can detoxify the butadiene

monoepoxide (BMO) nearly 20 times faster than the tissues derived from the mouse. These data are supportive of prior work in illustrating the extraordinary capacity for the mouse to produce and retain the toxic monoepoxide metabolite(s).

Body surface scaling implies that larger species (man, rat) would be more sensitive on a mg/kg basis to butadiene than the mouse. This is not consistent with the existing data on butadiene. The clear evidence -- including both metabolism and direct tumor data -- is that the mouse is the most sensitive species tested.

To illustrate this point further, the data from the OEHHA risk assessment demonstrate that the potency slope for lung tumors in the female mouse predicts a risk of 0.37/ppm, but the "worst case" potency slope derived from the rat data predicts a risk of 0.0036/ppm. Based on these data, the mouse is 100 times more sensitive than the rat. Scaling the mouse data using body surface scaling to predict a rat risk would go in the exact opposite direction. Thus, the bioassay results confirm that the body surface scaling assumption is not valid.

IV. OEHHA SHOULD USE THE INTERNAL CONCENTRATION OF THE REACTIVE BUTADIENE MONOEPOXIDE FOR THE MEASURE OF DOSE (INSTEAD OF ABSORBED BUTADIENE).

The Butadiene Panel continues to believe strongly that OEHHA should use the internal concentration of the reactive butadiene monoepoxide for the measure of dose.

All butadiene risk assessment documents, including the current OEHHA draft risk assessment, that discuss the metabolism and toxicity of butadiene clearly and correctly implicate the reactive butadiene epoxide metabolite(s) as the putative mutagenic and carcinogenic species. These metabolic schemes, without exception, point to the butadiene monoepoxide as the first metabolic product. It follows, therefore, that any pharmacokinetics model utilizing BMO would be superior to one based on external air or absorbed levels of butadiene. The fact that a full physiologic model has not yet been developed that includes the butadiene diepoxide (DEB) does not justify the preference of butadiene to BMO.

OEHHA has expressed concern that use of BMO for the measure of dose would not allow for consideration of the diepoxide or other epoxide metabolites. See p. 4-6. However, the evidence suggests that the mouse is also unusual in its ability to produce DEB. This is demonstrated by the known greater accumulation of BMO in the mouse, which is requisite for production of DEB, as well as recent in vitro evidence from CIIT that actual amounts of DEB are far greater in the mouse. Data by Csanady and Bond (1991) indicate that butadiene metabolism is six times higher in mice than in humans or rats, and the subsequent removal of the mutagenic epoxide is 4-fold more rapid in humans

than in rodents. In man, BMO is predominantly and rapidly metabolized by epoxide hydrolase to non-DNA reactive 1,2-dihydroxy but-3-ene. In contrast, the major BMO metabolic pathway in the mouse is slower and results in the formation of the mutagenic diepoxide. Thus, by using BMO for the measure of dose and disregarding species differences in DEB levels, OEHHA would likely overstate human cancer risks. (The basis for OEHHA's concern about "other epoxide metabolites" is unclear; the BMO and DEB are the only butadiene metabolites that have been implicated in the extensive studies of butadiene mechanisms of action.)

OEHHA also has expressed concerns regarding the adequacy of the available metabolism data, particularly the data reported by Sun et al. (1989) and Dahl et al. (1990). OEHHA appears to make three main points: (1) available data do not show a correlation between tissue concentrations of epoxide metabolites and observed incidences of carcinogenic lesions; (2) the data do not sufficiently account for observed differences in tumor incidences between species; and (3) the data allegedly demonstrate similarities between mice and monkeys. See OEHHA responses to the Panel's earlier comments (OEHHA comments nos. 6, 8, 11 and 22 at pages C-4 through C-11). The first two comments reflect unreasonable expectations of the OEHHA staff; it is not realistic to expect the data on species differences in metabolism to account for all differences in tumor incidences and locations with mathematical precision. The lack of perfect data on butadiene metabolism should not be used as a justification for disregarding the enormous body of evidence on butadiene metabolism and mechanism of action, all of which weighs heavily in favor of using BMO as the measure of dose. OEHHA's third point, concerning alleged similarities between the mouse and monkey data in Dahl et al. (1990), also is unfounded. This "similarity" is based on inappropriate scaling techniques (see comments above).

Instead of looking for reasons not to use the metabolism data, OEHHA should recognize that, when adjustments are made for metabolized dose and/or blood levels of epoxides across species, the risk estimates based on the mouse and rat tumor data become reasonably consistent. This fact suggests that use of the metabolized dose reduces uncertainties in the quantitative risk estimates. A demonstration (used here as an example) of this is presented in Table 1 below:

TABLE 1

	RAW POTENCY (unadjusted) (2 ppm)	ADJUSTMENT* METABOLISM (epoxide)
NIOSH MOUSE (FEMALE)	5.97/100	0.1/1000
OSHA RAT (FEMALE)	0.29/100	0.07/1000

* Adjustment to account for difference in the production of the butadiene monoepoxide in blood: factors of 590 in mice and 40 in rats (from Dahl et al. (1990) using primate data).

(From Cagen (1991)).

V. CARB SHOULD MAKE GREATER QUALITATIVE USE OF THE AVAILABLE DATA ON BUTADIENE METABOLISM AND MECHANISM OF ACTION.

If CARB is unwilling to use the available data on butadiene metabolism and mechanism of action for its quantitative risk assessment, then CARB at least should make greater use of these data for a qualitative assessment of the likely human cancer risks.

As already demonstrated, CARB's "best estimate" of the human cancer risks associated with exposure to butadiene is inconsistent with the available epidemiology data. CARB's "best estimate" is an upper bound estimate based on numerous worst case assumptions that are derived from general quantitative risk assessment guidelines, rather than butadiene-specific data. The available data on butadiene metabolism and mechanism of action, including data in the mouse, rat, monkey, and human, provide strong evidence that the B6C3F1 mouse is uniquely sensitive to the carcinogenic effects of butadiene. CARB's quantitative risk estimate, based on lung tumors in the mouse, therefore may overstate human cancer risks by a substantial margin. This should be expressly acknowledged whenever CARB presents its "best estimate" of human cancer risks.

In this regard, of greatest concern is the following statement in CARB's Executive Summary: "An estimated 3,936 1,3-butadiene-induced cancers statewide (based on the best value x 30 million people) are expected to occur at average ambient concentrations." This statement implies a level of precision which cannot reasonably be attributed to the risk estimate. If such a statement is made, it should be accompanied by an explicit recognition that: (1) This estimate is intended to be a conservative upper bound estimate of possible excess human cancer deaths. (2) CARB's "best estimate" is not necessarily the most plausible estimate. (3) CARB's "best estimate" is not consistent

with the results of available epidemiology studies. (4) Actual excess human cancer deaths from ambient levels of butadiene may be zero.

CONCLUSION

For the reasons presented in these comments and the supporting attachments, the Panel urges OEHHA to base its "best estimate" of butadiene human cancer risks on the rat bioassay, without surface area scaling, and using the internal concentration of the monoepoxide for the measure of dose. The Panel believes this approach would produce a more plausible "best estimate" of butadiene cancer risks. At the very least, OEHHA should expressly recognize the limitations of its own risk assessment methodology. Specifically, OEHHA should acknowledge that its current "best estimate" of butadiene cancer risks is an upper bound estimate that probably overstates human cancer risks by a wide margin. OEHHA should expressly state in the Executive Summary that the number of excess human cancer deaths from exposure to butadiene in ambient air may be zero.

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APPENDICES TO THE COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION BUTADIENE PANEL ON THE SRP VERSION OF THE DRAFT REPORT ON PROPOSED IDENTIFICATION OF 1,3-BUTADIENE AS A TOXIC AIR CONTAMINANT

I. Member Companies of the CMA Butadiene Panel

II. Comparison of Predicted and Observed Butadiene Human Cancer Risks -- Preliminary Comments on OEHHA Risk Assessment, prepared by Thomas B. Starr, Ph.D., of Environ Corporation

III. OSHA Post-Hearing Testimony of John F. Acquavella, Ph.D.

IV. Epidemiology Comments on CARB's Health Assessment, prepared by John F. Acquavella, Ph.D.

V. Statement of Stuart Z. Cagen, Ph.D., in Response to NIOSH Risk Assessment

VI. OSHA Post-Hearing Testimony of Michael G. Bird, Ph.D.

VII. Comments of Environ Corporation on NIOSH Risk Assessment (prepared by Thomas B. Starr, Ph.D.)

APPENDIX I

BUTADIENE PANEL
MEMBER COMPANIES

Amoco Chemical Company

American Petroleum Institute

Chevron Chemical Company

Dow Chemical USA

E.I. duPont de Nemours and Company

Eastman Kodak Company

Exxon Chemical Company

Lyondell Petrochemical Company

Mobil Chemical Company

Oxy Petrochemical, Inc.

Quantum Chemical Corporation

Shell Oil Company

Texaco Chemical Company

Union Carbide Corporation

APPENDIX II

COMPARISON OF PREDICTED AND OBSERVED
BUTADIENE HUMAN CANCER RISKS --
PRELIMINARY COMMENTS ON OEHHA RISK ASSESSMENT

Prepared by Thomas B. Starr, Ph.D.
Environ Corporation
December 6, 1991

OEHHA has called attention to the fact that the U.S. Environmental Protection Agency Carcinogen Assessment Group (CAG) implemented a consistency check for its "point" estimate of lifetime butadiene cancer risk using the Meinhardt et al. (1982) and Matanoski et al. (1982) studies of worker mortality in the styrene-butadiene rubber (SBR) industry. U.S. EPA (1985). In that consistency check, CAG combined its "point" estimate of butadiene potency with estimated exposure levels and the sample sizes of different worker groups to generate predicted numbers of extra deaths attributable to butadiene exposure assuming that the estimate of butadiene potency was accurate.

Fewer deaths were observed than were predicated in all but one of the six groups that CAG analyzed. U.S. EPA (1985). For example, in the study by Matanoski et al. (1982), for the worker group whose jobs last held were in the production category, there were significantly fewer observed deaths from lymphopoietic cancer than CAG's "point" estimate of butadiene potency predicted (11 deaths observed versus 20.6 predicted). CAG nevertheless concluded that its "point" estimate was not inconsistent with the observations, provided one assumed that the observed deficits in cancer deaths were due to an under ascertainment of deaths by the Matanoski et al. (1982). However, there was no basis for this assumption.

Nevertheless, the approach CAG used to evaluate the consistency of its risk estimates with epidemiologic observations is useful in objectively assessing the plausibility of different cancer potency estimates. Results from such quantitative comparisons of butadiene potency estimates have been reported previously by ENVIRON (1986, 1990 and 1991) and Acquavella (1990 and 1991). In each case, cancer potency estimates based on the mouse data have been shown to be inconsistent with the observations in the epidemiology studies.

While OEHHA also undertook such a comparison, it did so only for the maximum likelihood and upper bound potency estimates (0.0168 and 0.089 per ppm, respectively) based on malignant lymphoma incidence among male mice in the first NTP bioassay. NTP (1984). OEHHA did not perform a consistency check for its "best estimate" of cancer potency, 0.37/ppm, based on lung tumors in female mice in NTP-II. OEHHA also did not perform a consistency check for its "best" rat-based risk estimate (0.0098 per ppm), which was derived from the incidence of multiple significant tumors among female rats in the Hazelton rat study.

HLE (1981); Owen et al. (1987). It would have been far more appropriate to perform a consistency check against epidemiologic observations using these "best estimates" of butadiene cancer potency derived from the rat and mouse studies.

Tables 1 and 2 present the calculated probabilities of observing as few or fewer deaths from any cancer, respiratory tract cancer, or lymphopoietic cancer as were actually observed among the 3,124 SBR production workers as reported by Matanoski et al. (1990), assuming that the true cancer risks arising from this group's butadiene exposures were equal to the risks predicted with OEHHA potency estimates of 0.0098 (rat "best estimate") and 0.37 (mouse "best estimate") for 10, 5, 2 or 1 ppm butadiene, but with the exposure only for 10 or 50 working years and with follow up only for 21 of the 50 remaining years of life. As has been discussed elsewhere (ENVIRON, 1986, 1990, and 1991; Acquavella, 1990 and 1991), butadiene exposure levels in the SBR industry probably averaged 10 ppm or higher for these workers, so the predicted numbers of deaths appearing in Tables 1 and 2 most likely understate the extent of any inconsistencies between the observed number of cancer deaths and OEHHA's predictions.

Nevertheless, it is clear from Table 1 that the predicted risks obtained with OEHHA's "best" mouse-based potency estimate (0.37 per ppm) are altogether inconsistent statistically with the observed numbers of deaths in this SBR worker group for all cancers, respiratory tract cancers, or lymphopoietic cancer, even with exposure levels as low as 1 ppm. Many more cancer deaths should have occurred were OEHHA's "best" estimate actually correct. In contrast, as Table 2 indicates, OEHHA's "best" rat-based potency estimate yields predicted numbers of cancer deaths that are not demonstrably inconsistent with those observed.

It is important to note that significant inconsistencies between observed and OEHHA-predicted cancer deaths are readily apparent despite Matanoski et al.'s acknowledged understatement of the expected number of deaths in the absence of butadiene exposure (Matanoski et al. 1990), and despite not having considered the maintenance workers, who were also relatively heavily exposed, in this comparison. Had the subgroups of production and maintenance workers been combined appropriately, the inconsistencies between observed and OEHHA-predicted cancer deaths in this larger group would have been even more extreme than those presented in Table 1.

The epidemiologic observations thus indicate that OEHHA has significantly overstated the human cancer risks arising from butadiene exposure. In fact, OEHHA's "best" mouse-based estimate is altogether inconsistent with the actual observations in the production workers studied by Matanoksi et al. (1990), even assuming that butadiene exposures averaged about 1 ppm. While the epidemiologic data are not sufficiently powerful to categorically reject predicted risks as small or smaller than the estimate of 0.0098 per ppm which OEHHA derived from the HLE rat

bioassay, they are also entirely consistent with the far smaller risks that are predicted from a full and proper utilization of the butadiene absorption, retention, and metabolism differences that are now known to exist between rodents and primates. See Environ (1990, 1991).

TABLE 1

Consistency Check of CARB BD Cancer Risk Estimates

Predicted Versus Observed Cancer Deaths
Among 3,124 Production Workers (Matanoski et al., 1990)
Assuming a BD Cancer Potency of 0.37 per PPM
Lifetime Continuous Equivalent Exposure

	All Cancers	Respiratory Tract Cancers	Lymphopoietic Cancers
Observed Deaths	124	49	19
Predicted Deaths with 10 ppm	348.7	259.8	225.8
p-value	6.9×10^{-44}	6.2×10^{-58}	4.1×10^{-71}
Predicted Deaths with 5 ppm	242.2	83.9	119.3
p-value	3.8×10^{-17}	7.3×10^{-23}	4.3×10^{-30}
Predicted Deaths with 2 ppm	178.4	89.6	55.5
p-value	1.0×10^{-5}	2.0×10^{-6}	1.3×10^{-8}
Predicted Deaths with 1 ppm	157.1	68.3	34.3
p-value	0.0036	0.0088	0.0033

TABLE 2

Consistency Check of CARB BD Cancer Risk Estimates

Predicted Versus Observed Cancer Deaths
Among 3,124 Production Workers (Matanoski et al., 1990)
Assuming a BD Cancer Potency of 0.0098 per PPM
Lifetime Continuous Equivalent Exposure

	All Cancers	Respiratory Tract Cancers	Lymphopoietic Cancers
Observed Deaths	124	49	19
Predicted Deaths with 10 ppm	141.5	52.6	18.6
p-value	0.074	0.341	0.597
Predicted Deaths with 5 ppm	138.7	49.8	15.8
p-value	0.113	0.492	0.826
Predicted Deaths with 2 ppm	137.0	48.1	14.1
p-value	0.142	0.589	0.919
Predicted Deaths with 1 ppm	136.4	47.6	13.6
p-value	0.154	0.617	0.939

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UNITED STATES OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

DOCKET NO. H-041

SUPPLEMENTAL WRITTEN TESTIMONY

of

JOHN F. ACQUAVELLA, PhD

on behalf of

THE INTERNATIONAL INSTITUTE OF
SYNTHETIC RUBBER PRODUCERS, INC.

on

OSHA'S PROPOSED STANDARD
FOR 1,3-BUTADIENE

NOVEMBER 26, 1991

SUPPLEMENTAL WRITTEN TESTIMONY
OF JOHN F. ACQUAVELLA, PhD
ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S
PROPOSED STANDARD FOR 1,3-BUTADIENE

I am pleased to provide, on behalf of the International Institute of Synthetic Rubber Producers ("IISRP"), additional evidence and commentary on the health aspects of the Occupational Safety and Health Administration's ("OSHA's") proposed standard for 1,3-butadiene. My supplemental testimony addresses three distinct sets of issues.

Part 1 addresses the issue of short-term versus long-term workers, and responds to new arguments on this issue in recent comments that have appeared in the OSHA butadiene docket. This part of my supplemental testimony also provides additional information that I was asked to supply at the hearings.

Part 2 responds to the discussion of epidemiological issues in the posthearing comments on my testimony submitted by the National Institute for Occupational Safety and Health ("NIOSH").[1] As this part of my supplemental testimony demonstrates, several of the statements made by NIOSH regarding my reanalysis of the lymphopoietic cancer case-control study are misleading or in error.

Part 3 provides an epidemiological perspective on the NIOSH risk assessment. This part of my supplemental testimony

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[1] See Posthearing Comments of the National Institute for Occupational Safety and Health on the Occupational Safety and Health Administration's Proposed Rule on Occupational Exposure to 1,3-Butadiene (Sept. 27, 1991) (Ex. No. 90).

shows that projections from the NIOSH model are totally irreconcilable with the epidemiologic evidence for butadiene-exposed workers and therefore do not provide a valid estimate of the human health risks from butadiene exposure.

These three parts of my supplemental testimony along with the attached Appendices provide new information to assist OSHA's evaluation of the epidemiological data on butadiene. This information provides additional support for my overall conclusion, which I expressed at the hearing and in my written testimony, that the butadiene epidemiologic studies show favorable results that do not support a conclusion that butadiene causes cancer in humans.

UNITED STATES OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

DOCKET NO. H-041

SUPPLEMENTAL WRITTEN TESTIMONY OF JOHN F. ACQUAVELLA, PhD ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S PROPOSED STANDARD FOR 1,3-BUTADIENE

Part 1: Short-Term vs. Long-Term Workers and Additional Submissions for the Record

NOVEMBER 26, 1991

SUPPLEMENTAL WRITTEN TESTIMONY
OF JOHN F. ACQUAVELLA, PhD
ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S
PROPOSED STANDARD FOR 1,3-BUTADIENE

Part 1:
Short-Term vs. Long-Term Workers and Additional Submissions for the Record

During my OSHA hearing appearance, I was asked to supply further information by several members of the OSHA panel. In addition, new comments on the issue of the relative risks and exposures to short-term versus long-term workers have appeared in the butadiene docket. This supplemental testimony provides the requested information and addresses new issues in the recent comments.

SHORT-TERM vs. LONG-TERM WORKERS

In my OSHA testimony, I reviewed the epidemiologic evidence indicating that 1,3-butadiene workers did not show elevated cancer rates. For all three cohorts studied, cancer mortality was significantly lower than U.S. rates. Lymphopoietic cancer mortality, the focus of concern for OSHA, was not elevated overall or in long-term workers. Only some inconsistent findings in small short-term subgroups were found. The lack of elevated mortality rates for long-term workers does not support the hypothesis that butadiene is a carcinogen even at historical exposure levels in U.S. industry.

Dr. Landrigan submitted a March 6, 1991, letter to the docket (Ex. No. 82) arguing that "[s]ome short-term workers may

actually accrue greater total exposure than long term workers." This hypothesis is offered as an explanation for the lack of excess mortality among long-term workers and for the non-homogeneity of findings for short-term workers.

As indicated in my oral testimony, there is no evidence suggesting that short-term workers in the butadiene industry had higher exposures than their fellow workers during the same years who then continued in the industry. Indeed, there is the impression among industry supervisory personnel that short-term workers would have worked frequently in unskilled positions with fewer exposure opportunities, such as for example, baling rubber or conducting other non-process related manual work.

Dr. Landrigan's analogy is based on studies that involve worker exposure to metals in the form of respirable particles. This analogy is flawed for several reasons.

First, unlike volatile chemicals, certain metals can reside for long periods in the lung; hence, a short-term high-exposure results in continued exposure (at the target organ) as long as the metal is retained. The same cannot be said for butadiene, which is quickly metabolized and eliminated. Dr. Landrigan has not presented any examples that relate to chemical exposures (especially for volatile chemicals like butadiene), and I am aware of none.

Second, the issue of confounding exposures and differences in smoking and other lifestyle factors must be considered when comparing mortality rates for short-term versus long-term workers.

Third, in the studies cited by Dr. Landrigan, long-term workers show excess lung cancer. Indeed, this is true of virtually every established occupational carcinogen. In contrast, for butadiene, as pointed out at the OSHA hearings, workers who had long employment (even in highly exposed production and maintenance jobs) show no excess mortality from lymphopoietic or any other cancers.

Fourth, the cited studies, when read carefully, actually are inconsistent with Dr. Landrigan's argument. I describe each below:

Ott et al. (1974) found an increasing association for lung cancer with duration of employment and cumulative exposure to chemicals. For example, Ott (p. 253) reports that 12% (16/138) of decedents were lung cancers among those employed less than one year, while 27% (12/45) were lung cancers among those employed more than one year. While these proportions are not directly comparable (due to presumed age differences), these data, when properly age-adjusted, would almost certainly be contrary to the hypothesis of a greater effect in shorter term workers.

Infante et al. (1980) concentrated on a subgroup of beryllium workers whose disease state qualified them for the beryllium registry. No duration of employment analyses were presented, but I presume that the citation of this study relates to the lung cancer excess among these characterized with acute disease (primarily those with acute bronchitis or pneumonitis or,

in the absence of a clear diagnosis, those whose illness occurred within one year of initial exposure), but not those characterized with chronic disease. Two points detract from this argument. First, the acute group is not a short-term worker subgroup - only those few workers with unclear diagnostic information are characterized as acute based on short-term employment. Second, as Infante pointed out, the extremely high mortality from non-malignant respiratory disease for the chronic group (presumably due to high case fatality as a consequence of extremely high exposures) was so extensive (21% of deaths) as to preclude the subsequent development of lung cancer (see p. 40). A similar phenomenon is known to have occurred among early asbestos workers. Furthermore, other studies have shown excess lung cancer in long-term beryllium workers.

Wagoner et al. (1980) looked at a cohort of 3055 beryllium workers at a plant in Pennsylvania. SMRs were very similar for those employed less than or more than five years, especially for those with long latency (SMRs of 187 and 174, respectively, for workers with 25+ years latency). Wagoner pointed out that the destruction of work records in 1968 precluded updating employment histories from 1968-1975 (the study end date), so workers tended to be classified incorrectly into shorter employment durations (see p. 29). Hence, in this study there is little difference in findings between short-term and long-term workers; and there is an acknowledged bias toward underestimating duration of employment.

Thun et al. (1985) studied 602 white males at a cadmium recovery plant. In the abstract to this paper, the authors state clearly that there were no lung cancers among those employed less than two years. Later, in an analysis excluding workers with arsenic exposure (Table 4 and related text), the authors relate that workers employed less than two years had 0 observed versus 3.87 expected, while SMRs were approximately 200 for those employed 2-9 years, 10-19 years, and 20+ years. Again, these findings are markedly different than those seen for butadiene workers -- where there is no mortality excess for long-term workers.

Interestingly, the authors also provide evidence that exposure was indeed higher for longer term workers (see p. 332) based on cadmium biomonitoring. For workers employed less than two years, approximately 30% had urinary cadmium levels of 20 µg/l; while that level was exceeded for 81% of the total population (thus, the exclusion of those employed less than two years from the total population result would demonstrate that more than 81% of longer term workers had urine levels of at least 20 µg/l). Hence, it is clear that longer term workers had more cadmium exposure than short-term workers. The same is almost certainly true for butadiene in monomer and polymer production.

In sum, there is no precedent for occupational carcinogenic effects being seen only in short-term workers or for short-term workers having higher exposures than long-term

workers. Such a position is unprecedented and has no scientific basis.

ADDITIONAL SUBMISSIONS FOR THE RECORD

During my testimony I was asked to submit several items for the record. Accordingly, attached as Appendices to my supplemental testimony are:

(1) My July 24, 1989, letter to Dr. Matanoski requesting information on control selection in the case-control study she authored with Dr. Santos-Burgoa (Appendix A).

(2) Dr. Santos-Burgoa's dissertation, which provides some detail on the case-control study not included in the Final Report already in the OSHA docket (Appendix B). Regarding the protocol for the study, I checked my files and with my colleagues on the Epidemiology Subcommittee and found no indication that a copy was ever provided to IISRP.

(3) Four articles that have been referenced in the OSHA proceeding:

(a) H. Checkoway et al. (1984). "An Evaluation of the Associations of Leukemia and Rubber Industry Solvent Exposures." Am. J. Indus. Med. 5:239-249 (Appendix C);

(b) H. Checkoway & T. Williams. (1982). "A Hematology Survey of Workers at Styrene-Butadiene Synthetic Rubber Manufacturing Plant." Am. Indus. Hyg. Assn. J. 43:164-169 (Appendix D);

(c) A. Smith & L. Ellis. (1977). "Styrene Butadiene Rubber Synthetic Plants and Leukemia." J. Occup. Med. 19:441 (letter to editor) (Appendix E); and

(d) R. Rodger et al. (1987). "Factors Influencing Haematological Measurements in Healthy Adults." J. Chron. Dis. 40:943-47 (Appendix F).

(4) Information indicating, as I testified, that many of the workers at the butadiene monomer facility built during World War II were borrowed from existing petrochemical facilities in the area, including:

(a) A pamphlet written in the late 1970s by the Port Neches Butane Products Co., about the butadiene monomer plant now run by Texaco and studied by Drs. Downs and Divine (Appendix G); and

(b) Examples of a few employee records from this plant indicating prior employment in the parent company petrochemical facilities (Appendix H).

I have also ascertained the answers to two questions posed to me at the hearing about the SBR industry:

(1) The dates of operations for styrene butadiene rubber (SBR) plants in North America are shown in Table 1 below:

Table 1: North American SBR Plants

	ORIGINAL COMPANY NAME	SITE	START-UP YEAR
✓	National Synthetic Rubber Corp.[1]	Louisville, KY	1943
✓	Copolymer Corp.	Baton Rouge, LA	1943
✓	Firestone	Lake Charles, LA	1943
	Firestone[2]	Port Neches, TX	1943
✓	General Tire[3]	Baytown, TX	1943
✓	General Tire	Odessa, TX	1957
	BF Goodrich[4]	Louisville, KY	1942
✓	BF Goodrich[5]	Borger, TX	1943
	BF Goodrich[6]	Port Neches, TX	1943
✓	Polymer Corp.[7]	Sarnia, Canada	1943
✓	Goodyear	Houston, TX	1943
	Goodyear[8]	Torrance, CA	1943
	Goodyear	Beaumont, TX	1961
	U.S. Rubber Co.[9]	Naugatuck, CT	1942
	U.S. Rubber Co.[10]	Institute, WV	1943
	U.S. Rubber Co.[11]	Los Angeles, CA	1943

✓ Plant included in Matanoski study.

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1 Now American Synthetic Rubber Company.

2 Now part of Ameripol Synpol (North plant).

3 Sold to Ashland Oil, subsequently closed in 1977.

4 Discontinued SBR production in 1947.

5 Sold to Phillips Petroleum, subsequently closed in 1984.

6 Now part of Ameripol Synpol (South plant).

7 Now Polysar Rubber Corporation.

8 Sold to 3M and then Shell, subsequently closed in 1969.

9 Now Uniroyal Chemical Company, discontinued SBR production in 1974.

10 Sold to Union Carbide in 1955, SBR production discontinued shortly thereafter.

11 Sold to Goodyear, 3M and then Shell, subsequently closed in 1969.

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(2) As the above list indicates, almost all the operating SBR plants in 1976 were included in the Matanoski cohort study. The only exceptions were the BF Goodrich plant and Firestone plants in Port Neches, which were not included in the Matanoski study. However, these two plants now form the Ameripol Synpol facility and comprised the study population in the Meinhardt study.

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P.F. Infante et al. (1980). "Mortality Patterns from Lung Cancer and Neoplastic Respiratory Disease Among White Males in the Beryllium Case Registry." Envtl. Res. 21:35-43.

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J.K. Wagoner et al. (1980). "Beryllium: An Etiologic Agent in the Induction of Lung Cancer, Nonneoplastic Respiratory Disease, and Heart Disease Among Industrially Exposed Workers." Envtl. Res. 21:15-34.

UNITED STATES OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

DOCKET NO. H-041

SUPPLEMENTAL WRITTEN TESTIMONY OF JOHN F. ACQUAVELLA, PhD ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S PROPOSED STANDARD FOR 1,3-BUTADIENE

Part 2: Response to NIOSH Posthearing Comments on Acquavella Testimony Regarding the Case-Control Study

NOVEMBER 26, 1991

SUPPLEMENTAL WRITTEN TESTIMONY
OF JOHN F. ACQUAVELLA, PhD
ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S
PROPOSED STANDARD FOR 1,3-BUTADIENE

Part 2:
Response to NIOSH Posthearing Comments on Acquavella Testimony Regarding the Case-Control Study

NIOSH (NIOSH 1991) has offered comments on my reanalysis of the lymphopoietic cancer case control study by Matanoski et al. (Acquavella 1990). Several of these comments are misleading or in error.

In my written OSHA testimony, I commented on the unusual analysis -- based on log butadiene rather than actual butadiene exposures -- presented by the authors of the lymphopoietic cancer case control study (Matanoski et al. 1989). Specifically, I made two points about basing the analysis on the mean log butadiene score:

(1) Textbooks on case control methodology prescribe no distributional requirement (i.e., normality) for the underlying exposure data used to calculate an odds ratio ("OR") (Rothman 1986; Schlesselman 1982; Kleinbaum et al. 1982); and

(2) The unnecessary logarithmic transformation did not produce a normal distribution of the butadiene exposure scores and only served to change the cutpoint for calculating the OR. Therefore, it would have been prudent,

at a minimum, also to report the OR for the actual, non-transformed, butadiene exposure data. The respective ORs were 7.6 (mean log exposure) and 0.9 (mean actual exposure). Clearly, the choice of cutpoint determines the interpretation of the findings from these dichotomous analyses.

NIOSH has taken issue with these criticisms. First, they mention (p.2, lines 6-9) that I did not give the normality statistics to support my statement that the log butadiene data were not normally distributed. The normality statistics for the 110 exposure values (SAS version 6.03, 1988) are:

Actual butadiene data: Shapiro-Wilk statistic (W) = 0.773, p value < 0.0001, skewness 1.62, kurtosis 2.13.

Log butadiene data: Shapiro-Wilk statistic (W) = 0.805, p value < 0.0001, skewness 0.975, kurtosis 0.344.

Clearly, neither distribution is normal or near normal.

Second, NIOSH suggests (p.2, lines 9-12) that a normal distribution of the actual exposure data was implied in my analysis based on the mean of the actual butadiene exposure data. This is simply not true. As stated previously, there is no requirement for normality of exposure data in case control studies. The sole difference in analyses based on the actual or log transformed butadiene data is an arbitrary choice of an exposure value for dichotomizing workers by exposure. NIOSH made this very point subsequently (p.2, lines 13-15):

"The choice of cutpoints for categorizing exposures in epidemiologic analyses relies, to some extent, on judgments for which there are no generally agreed-upon principles."

My reason for presenting the analysis based on the actual butadiene data was that it illustrated the variability in the estimation of the OR in the case control study (Matanoski et al. 1989) -- a point which should have been a major focus of discussion for the authors of this study and/or scientists charged with evaluating this study. Such variability hindered the estimation of the ratio of leukemia rates associated with butadiene exposure. Yet, this issue was not discussed at all by the authors of the study or by OSHA.

Third, the NIOSH authors imply that the variability seen in the ORs for the log transformed versus the actual data analyses (7.6 versus 0.9) is typical in case control studies (p.2, lines 13-16):

"It is well recognized that the choice of cutpoints may dramatically alter the findings, and that appears to be true in this case." (emphasis added)

I believe that this statement is clearly misleading. While there are situations where a slight change in cutpoint results in a modest change in the OR, I am not aware of any previous situation where changing the dichotomization point slightly, as illustrated in my analysis, changes the OR from a value indicative of a

strong association (7.6) to one indicative of no association (0.9). In my testimony, I quoted from Rothman's textbook on this issue (Rothman 1986, p.135):

> "... the shift of a boundary in categorization rarely has a substantial effect on the magnitude of an estimate and then only because of a large random error component."

In the absence of examples that demonstrate OR variability analogous to that seen in the Matanoski et al. case control study, NIOSH's opinion on this point is not credible.

NIOSH mentions the presence of a significant linear trend with butadiene exposure in a categorical analysis as strong evidence of a relationship between butadiene exposure and leukemia (p.2, lines 26-28 and lines 40-42). It is noteworthy that such a trend is not seen in analyses based on evenly balanced tertiles, quartiles, or quintiles (viz. exposure categories based on equal numbers of controls or cases and controls). For example, Dr. Philip Cole in his testimony gave ORs for three evenly balanced exposure levels (1.0, 5.3, 2.3) that did not indicate a linear relationship with dose (Cole 1990). One noteworthy property of the categorical analysis cited by NIOSH is that the 26 cases and 84 controls were apportioned unevenly into seven exposure levels, and the individual point estimates in many of the categories were based on so few cases and/or controls as to be unreliable. Again, it is the choice of exposure cutpoints that dictates the presence or absence of a significant relationship in this case control study.

NIOSH also advocates the use of a continuous butadiene exposure score in logistic regression as a more powerful test of linear trend and points out that such an analysis produced a significant coefficient for butadiene exposure (p.2, lines 28-35). However, such an analysis is considered to be inappropriate in most epidemiologic situations since it carries the inherent assumption that each exposure increment multiplies the OR by a constant factor (see Greenland 1979; Rothman 1986). Such an assumption is rarely ever appropriate and, in this case, is clearly inconsistent with the leukemia mortality seen in the base population for the case control study (22 observed, 22.8 expected) and with Dr Cole's exposure level analysis.

Finally, NIOSH mentions that overmatching in the case control study may have resulted in an underestimate of the OR for butadiene exposure. However, Dr. Cole demonstrated in his OSHA testimony (Cole 1991) that the case control odds ratio of 7.6 (along with the 60% control exposure prevalence) is incompatible with the lack of any leukemia excess in the cohort study for this worker population (i.e., 22 observed, 22.8 expected). Specifically, he presented the following data:

Leukemia deaths predicted in the SBR workers cohort study from the case control results; odds ratio = 8

% cohort exposed	predicted deaths in cohort study
25%	63
50%	103
60%	119

(adapted from Cole 1991)

The incompatibility would be even greater for the higher OR, which presumably would have resulted in the absence of overmatching.

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UNITED STATES OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

DOCKET NO. H-041

SUPPLEMENTAL WRITTEN TESTIMONY OF JOHN F. ACQUAVELLA, PhD ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S PROPOSED STANDARD FOR 1,3-BUTADIENE

Part 3: An Epidemiologic Perspective on the NIOSH Risk Assessment for Butadiene

NOVEMBER 26, 1991

SUPPLEMENTAL WRITTEN TESTIMONY
OF JOHN F. ACQUAVELLA, PhD
ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S
PROPOSED STANDARD FOR 1,3-BUTADIENE

Part 3:
An Epidemiologic Perspective on the NIOSH Risk Assessment for Butadiene

NIOSH has recently completed a risk assessment based on tumor incidence data from a low dose butadiene $B_6C_3F_1$ mouse bioassay (Melnick et al. 1990). Based on the most sensitive target site in the $B_6C_3F_1$ mouse - lung tumor incidence - the resulting estimate of risk at 2 ppm for 45 years exposure was 597 excess cancers per 10,000 workers per lifetime - or 5.97 per 100 (Dankovic et al. 1991). This prediction does not even vaguely resemble actual human experience in butadiene-related industries where, on an industry-wide basis, all cancer and lung cancer mortality rates are significantly lower than general population rates and lymphopoietic cancer rates are similar to general population rates (Acquavella 1990; Cole 1990).

The discrepancy between the NIOSH model and worker experience is best illustrated by the mortality findings for the Texaco subcohort of 1,066 butadiene monomer workers first employed before 1946 (Divine 1990). These workers were employed at, or soon after, industry startup and had experience working during World War II when overtime was extensive and exposure conditions resulted in higher exposures than were likely to result from recent plant operations. These workers have been followed for mortality outcomes from first employment during the

period 1943-45 through the end of 1985 (an average 41.5 years for living workers) -- almost a lifetime followup period for risk assessment purposes. Fifty-six percent of these workers are deceased (Divine 1990). Average duration of employment for these workers was 12.4 years (B. Divine, personal communication).

I will evaluate the NIOSH risk projections for these Texaco workers in terms of all cancers, lung cancer, and lymphopoietic cancers. These cancer sites were selected for the following reasons:

(1) All cancer - Butadiene was associated with malignancies of various organs in the $B_6C_3F_1$ mouse studies (Huff et al. 1985; Melnick et al. 1990) and could be presumed by some to have an analogous effect on workers.

(2) Lung cancer - The lung was the most sensitive cancer site in the recent $B_6C_3F_1$ mouse study (Melnick et al. 1990), and one could argue that inhalation of butadiene and metabolism in the lung is qualitatively similar across species.

(3) Lymphopoietic cancer - This site was seen in excess at 200 ppm and higher doses in the $B_6C_3F_1$ mouse studies (Huff et al. 1985; Melnick et al. 1990), and there has been debate about butadiene and lymphopoietic cancers in the epidemiologic literature.

The findings for these cancer sites in the Texaco study are listed in Table 1.

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Table 1
Mortality Findings for Texaco World War II Subcohort

	observed	expected	SMR	95% CI
All cancer	106	140.9	75	62-91
Lung cancer	36	44.2	82	57-113
Lymphopoietic	16	12.7	126	72-205

It is clear upon inspection that these data conflict with the NIOSH risk assessment. There is a significant 25% deficit of all cancer mortality, and lung cancer and lymphopoietic cancers are only slightly lower or higher than general population rates, respectively. The following analyses quantify the extent of the conflict.

The NIOSH excess risk projection of 5.97 per 100 is based on 2 ppm exposure for 45 years or 90 ppm years. Past exposures are not documented for the Texaco workers, but we can assume that exposures exceeded the proposed OSHA standard of 2 ppm and the current Threshold Limit Value (TLV) of 10 ppm since 1000 ppm was the workplace exposure limit during the early decades of this industry. However, actual exposures were maintained well below 1000 ppm to minimize the danger of fires or explosions. Therefore, it seems reasonable to evaluate risk projections from the NIOSH model for a range of average exposures from a maximum of 20 ppm (i.e., 10 times the proposed OSHA

standard or 2 times the current TLV) to a minimum of 2 ppm with an intermediate value of 10 ppm.

The calculation of predicted cancers for these workers takes the general form:

predicted excess cancers + expected cancers

The actual calculation is as follows:

[(average ppm X years employed)/90 ppm years] X 1066 workers X (5.97 excess cancers/100 workers)] + expected cancers = predicted cancers

In addition, a correction factor should be incorporated into the calculation to compensate for the slightly less than lifetime followup (e.g., 41.5 years/45 years) for the 44% of the Texaco work force who were still alive at the end of the study follow-up period (correction factor = (1 -((41.5/45) X (0.44)) = 0.97).

Thus, for all cancers assuming a 20 ppm average exposure, the predicted number of cancers equals:

[((20 ppm X 12.4 years employed)/90 ppm years) X 1066 workers X (5.97 excess cancers/100 workers) X (0.97)] + 140.9 expected deaths = 311.0 predicted cancers

Predicted cancers at 20 ppm, 10 ppm, and 2 ppm are given in Table 2 along with the probabilities of seeing the observed number of deaths or fewer.

Table 2
Predicted Deaths for Texaco Subcohort

A. All Cancers (actual Texaco data = 106 observed)

ppm	NIOSH predicted	probability of observed or fewer deaths
20	311.0	1.9×10^{-41}
10	226.0	4.0×10^{-19}
2	157.9	7.3×10^{-6}

B. Lung Cancer (actual Texaco data = 36 observed)

20	214.3	2.3×10^{-51}
10	129.3	2.7×10^{-22}
2	61.2	3.5×10^{-4}

C. Lymphopoietic Cancer (actual Texaco data = 16 observed)

20	182.8	3.3×10^{-57}
10	97.8	1.3×10^{-24}
2	29.7	4.5×10^{-3}

These analyses illustrate that the cancer predictions from the NIOSH risk assessment model are totally inconsistent with human experience in a high exposure, long followup subgroup of butadiene workers. For example, assuming these workers averaged 10 ppm butadiene exposure, the NIOSH risk assessment model predicts 226 deaths from all cancers, but only 106 were

observed. The probability of seeing only 106 deaths or fewer when 226 are predicted is 4×10^{-19}. This incredibly small probability is a measure of how well the risk assessment model fits the data it was intended to predict. (Probabilities less than 0.05 indicate that the model does not provide an adequate fit to the data.) Predictions at 10 ppm for lung cancer and lymphopoietic cancers show similar lack of fit: lung cancer - 36 observed, 129.3 predicted, probability = 3×10^{-22}; lymphopoietic cancers - 16 observed, 97.8 predicted, probability = 1×10^{-24}. Predictions at 2 ppm -- which assume that exposures 30 to 40 years ago did not exceed the current OSHA proposed standard -- still overpredict mortality from all cancer (probability = 7.3×10^{-6}), lung cancer (probability = 3.5×10^{-4}) or lymphopoietic cancers (probability = 4.5×10^{-3}). Thus, these analyses provide a high degree of empirical evidence that the NIOSH risk assessment model greatly overestimates risk for workers exposed to 1,3-butadiene.

The reason for the lack of correspondence between the NIOSH risk projections and actual human experience was discussed extensively in the OSHA hearings -- the $B_6C_3F_1$ mouse is hypersensitive to the carcinogenic effects of 1,3-butadiene (see Bird 1990; Hinderer 1990; Starr 1990). Accordingly, risk assessments based on the $B_6C_3F_1$ mouse data do not provide a valid basis to evaluate the risk for workers at or near the proposed OSHA standard. An alternative approach is clearly warranted.

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APPENDIX IV

EPIDEMIOLOGY COMMENTS ON CARB'S HEALTH ASSESSMENT

Prepared by
John F. Acquavella, Ph.D.
December 6, 1991

CARB's review of the epidemiology has incorporated many of the comments previously submitted by industry representatives. However, CARB's current evaluation of the butadiene epidemiologic data selectively highlights positive findings, neglects important negative findings, and the overall interpretation relies on a number of unproven assumptions. These assumptions include a uniform reduction in butadiene exposures across industry after 1945, a lack of correlation between employment duration and cumulative exposure, and a biological consistency of varied lymphopoietic cancer findings across studies due to clinical similarity and/or misdiagnosis on death certificates. CARB also evaluates the recent lymphopoietic cancer case control study (Matanoski et al. 1989) exclusive of the markedly conflicting findings from the base cohort study (Matanoski et al 1990) and misrepresents the hematological effects findings among styrene butadiene rubber (SBR) workers (Checkoway and Williams 1982). Finally, CARB continues to give undue attention to studies of tire manufacturing populations, in which solvents, not butadiene, have previously been associated with elevated rates of lymphatic leukemia (McMichael et al 1976, Andjelkovich et al. 1977, Monson and Fine 1978, Checkoway et al. 1984).

Exposure before/after 1945

CARB asserts that exposures were reduced substantially throughout the SBR industry after 1945 and argues that elevated lymphopoietic cancer rates among World War II workers are more important for assessing carcinogenicity than trends in lymphopoietic cancer rates by duration of employment. CARB's hypothesis about exposures may or may not be true, but since it is a key argument in their evaluation of the epidemiologic data it should be evaluated critically along with the relevant studies.

Exposures before and after 1945 (for 20 or so years) are unknown. Workplace exposure monitoring for butadiene began in the 1970s. Thus, there are no exposure measurements to verify a substantial reduction in exposures after 1945, though this concept is intuitively appealing due to polymerization process changes at some, if not all, of the SBR plants. CARB should verify that process changes occurred immediately after 1945 at all SBR plants if this is a key assumption for their interpretation of the epidemiologic data. However, even if the implementation of process changes reduced exposures for polymerization areas of all SBR plants from 1946 onward, it is unlikely that there would have been a corresponding reduction in exposure for several of the high exposure jobs in non polymerization areas including: monomer loading/unloading, polymer sampling, maintenance activities, laboratory analysis, etc. In addition, there were no corresponding process changes in

the only butadiene monomer plant studied to date (Divine 1990, B. Divine, personal communication). Thus, CARB's hypothesis of a uniform exposure reduction across all jobs in industry is possibly only valid for workers employed in SBR polymerization. CARB should reconsider their interpretation of the epidemiology data under a more limited exposure reduction scenario and excluding monomer production workers.

Second, CARB's conclusion of a carcinogenic effect among workers employed prior to 1946 is not consistent with the available epidemiologic data. For example, Matanoski et al. did not see elevated lymphopoietic cancer rates in their World War II subcohort (Matanoski et al. 1988). In Meinhardt et al., the results were internally inconsistent. Only very short term workers hired before 1946 showed a leukemia excess. Specifically, two of the five leukemia decedents in Plant A had extremely short employment durations and times from first employment to death (e.g. employment periods of 6 months and 1.5 years and induction/latency periods of 3 years for both decedents), while there was no accompanying excess in their long term co-workers. The latter group would have had the high exposures characteristic of World War II operations and opportunity for subsequent exposures from continued employment. The pattern of very short latency leukemias does not appear to be of etiologic importance since it has no analogy in the other much larger SBR workers study (Matanoski et al. 1990), where only one leukemia death occurred within 10 years of first employment (an employee hired

in the 1970s). So, the Meinhardt findings are, at a minimum, internally inconsistent for workers employed before 1946. Similarly, the Divine study (Divine 1990) of butadiene monomer workers did not have a lymphosarcoma excess in long term World War II workers since there were no lymphosarcoma deaths in any worker employed more than 10 years in this study, and there was no leukemia excess among World War II workers. Thus, the varying short term worker findings, in the absence of findings among their long term colleagues, suggest the possibility that confounding exposures, not butadiene, were the responsible etiologic factors.

The Texaco World War II subcohort findings are important because they represent workers with the longest follow-up across studies (41.5 years) and who averaged 12.4 years employment (Divine, personal communication). Findings for these workers provide an important perspective, particularly for concerns about all cancer and lung cancer from butadiene exposure. As indicated in the table below, these workers had a significant deficit of all cancers and a low rate of lung cancer. Similar findings are seen in Meinhardt et al. (1982) and Matanoski et al. (1990).

Mortality findings for Texaco World War II subcohort

	observed	expected	SMR	95% CI
all cancer	106	140.9	75	62-91
lung cancer	36	44.2	82	57-113
lymphopoietic	16	12.7	126	72-205
lymphosarcoma	7	2.6	269	108-555

leukemia	6	5.5	112	41-244
other lymphatic	2	3.4	59	7-212

from Divine 1990

These data demonstrate that all cancer and lung cancer are not likely outcomes of long term occupational exposure to butadiene. The lymphopoietic cancer findings for these workers are essentially null, with the exception of lymphosarcoma and, as mentioned previously, the lymphosarcoma excess is confined (paradoxically) to short term workers.

CARB mentioned that the lymphopoietic cancer findings from the Matanoski et al. cohort study (Matanoski et al. 1988 and 1990) are less useful because the omission of early workers (viz. World War II workers) at four plants with incomplete records might have obscured a carcinogenic effect of butadiene exposure. This concern can be evaluated by reviewing the SMRs for the four plants in this study with complete records - plants where the "early workers" have been completely enumerated. SMRs for these plants were presented for this study (Matanoski 1988). These data show a pattern of extremely low SMRs including significant deficits of total mortality and cancer mortality, and borderline significant deficits of lymphopoietic cancers ($p = 0.06$) and lymphosarcoma ($p = 0.06$). Leukemia mortality was only 74% of expected values.

SMRs for plants with complete records

cause of death	obs	exp	SMR	95% CI
all causes	1188	1567.2	76	72-80
all cancers	233	313.2	74	65-85
lymphopoietic cancer	24	35.0	69	44-102
lymphosarcoma	2	7.0	29	3-103
leukemia	10	13.5	74	36-136

from Matanoski 1988

These data do not support CARB's contention that exclusion of early workers from four of the eight plants in this study is likely to mask a relationship between butadiene and disease in this study.

Varying lymphopoietic cancer findings across studies

CARB dismisses the criticism that variation in health endpoints across studies detracts from a causal interpretation for butadiene and lymphopoietic cancer. This issue has been discussed in detail by Cole (Cole 1990) at the OSHA hearings and CARB should consider and respond to his specific criticisms on this matter before adopting this viewpoint.

CARB's basis for disregarding the heterogeneity of the lymphopoietic cancer findings seems to be comments by Matanoski et al. (1990) and Landrigan (1990) that the individual lymphopoietic cancers are related tumors (viz. butadiene may cause all types of lymphopoietic cancer) and that there is diagnostic overlap and changing nomenclature over time. These

points are logically inconsistent with the findings for butadiene workers and they need to be evaluated critically.

First, if butadiene was a common etiologic factor for several or all lymphopoietic cancers, it is unlikely that there would be marked variability in findings across studies. Rather, there would tend to be a general lymphopoietic cancer excess for all sites rather than excesses and deficits of specific lymphopoietic cancers across studies. Such is not the case.

The second issue, diagnostic overlap, is not a credible explanation for the epidemiologic findings since it also occurs in the general population - the comparison population for the butadiene cohort studies. So, for example, a doubling of the multiple myeloma rate among butadiene workers with some misdiagnosis would be compared to the general population rate also impacted by misdiagnosis. As long as the misdiagnosis is relatively comparable for workers and the general population, the SMR should not be affected greatly.

Third, diagnostic variability differs by type of lymphopoietic cancer (see table below) as illustrated by a comparison of cancer incidence and death certificate data for cases from the Third National Cancer Survey 1969-1971 (Percy et al. 1982). Therefore, diagnostic variability will have little effect on lymphopoietic cancers with a high percent confirmation.

Confirmation rates for lymphopoietic cancers on death certificates -- based on the Third National Cancer Survey

primary site	#	% confirmed
Non-Hodgkin's lymphoma	1562	88.4
Multiple myeloma	699	98.1
Lymphocytic leukemia	743	86.3
Myeloid leukemia	1107	92.2
Monocytic leukemia	98	53.8
Other & unspecified leukemia	204	34.3

from Percy et al. 1982

Finally, most of the lymphopoietic cancer deaths in these studies happened within the last 10-15 years of the respective study periods, and diagnostic specificity has improved with time.

Taken together, these points would argue that the relationships of the lymphopoietic cancers or the extent of misdiagnosis is unlikely to be a suitable explanation for the heterogeneous lymphopoietic cancer findings seen in the butadiene epidemiologic literature.

Interpretation of the lymphopoietic cancer case control study

The findings from the SBR workers lymphopoietic cancer case control study (Matanoski et al. 1989) are irreconcilable with findings for the cohort study of the same population (Matanoski et al 1990). CARB should evaluate these two related studies together to determine whether the strong leukemia/butadiene

association reported in the case control study can be rationalized with the lack of a leukemia excess in the base cohort study. In addition, two reanalyses of this study were presented at the OSHA hearings which showed markedly different findings than those presented by the authors (see Acquavella 1990, Cole 1990). Two issues were identified as critical in interpreting this study: 1) the selective analysis presented by the authors; and 2) the incompatibility of the case control and base cohort findings.

The analysis of the case control study was quite selective and masked striking internal inconsistencies in the odds ratio (OR) estimates related to butadiene exposure (Acquavella 1990). Most of the analyses presented in the study report (Matanoski 1989) categorized workers as either exposed or unexposed based on the mean of the <u>logarithms</u> of the butadiene exposures. The conclusions from this study were based on these analyses. The authors did not mention that an analysis based on the actual, non-transformed, butadiene data, instead of the logarithms of the data, would have resulted in substantially lower ORs - consistent with the conclusion of no association between leukemia and butadiene exposure. Furthermore, even exposure level analyses at the highest exposure level resulted in lower estimates of the OR than the mean log butadiene analysis (Cole 1990).

The rationale given in this report for employing a logarithmic transformation was "... due to the skewing of the data." That is, the butadiene exposure data were not normally

distributed and the investigators attempted to normalize the butadiene exposure distribution. The advisability of this transformation was questionable since textbooks on case control methodology prescribe no such normality requirement for the underlying exposure data used to calculate ORs (Rothman 1986, Schlesselman 1982, Kleinbaum et al. 1982). Further, the logarithmic transformation did not produce a normal distribution of the butadiene exposure scores (Acquavella 1991) as indicated by the following normality statistics:

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actual butadiene data: Shapiro-Wilk statistic (W) = 0.773, p value < 0.0001, skewness 1.62, kurtosis 2.13

log butadiene data: Shapiro-Wilk statistic (W) = 0.805, p value < 0.0001, skewness 0.975, kurtosis 0.344

from Acquavella 1991

All that resulted from the logarithmic transformation was a slight variation of the cutpoint for dichotomizing cases and controls. Thus, it would have been prudent, at a minimum, also to report results for the actual, non-transformed, butadiene exposure data (and to discuss any inconsistencies).

The results of analyses based on the actual butadiene data conflict markedly with the analyses based on the logarithmic data. Specifically, the two analyses yielded the following:

OR $_{\text{mean log butadiene scores}}$	= 7.6 (1.6 - 35.6)
OR $_{\text{mean actual butadiene scores}}$	= 0.9 (0.3 - 2.6)

(from Acquavella 1990)

The striking difference between analyses suggests a large random error component in the reported OR of 7.6 for butadiene and leukemia and points out the unreliability of conclusions based on that result.

In light of this variability, Cole conducted an exposure level analysis with controls distributed evenly by exposure tertiles - an unbiased method of exposure categorization (Cole 1990). These analyses revealed an irregular exposure response pattern with a precipitous decline in the OR for the highest exposure category (i.e., ORs 1.0, 5.3 and 2.3 for the lowest, intermediate and highest exposure categories, respectively). The marked decline in ORs from the intermediate to the highest exposure category again indicates a large random error component in this study.

Exposure level analyses were presented by Matanoski et al. (Matanoski et al. 1989) although they received less emphasis then the dichotomous analyses. In fact, the authors reported a significant linear trend with butadiene exposure in a categorical analysis. This categorical analysis apportioned the 26 cases and 84 controls unevenly into seven exposure levels and the

individual point estimates in many of the categories were based on so few cases and/or controls as to be unreliable. A trend by exposure level was not seen in analyses based on evenly balanced tertiles, quartiles, or quintiles (viz. exposure categories based on equal numbers of controls or cases and controls as from Cole 1990). Again, it seems that the choice of exposure cutpoints dictates the presence or absence of a significant relationship in this case control study.

The authors also used a continuous butadiene exposure score in logistic regression and found a borderline significant trend. However, such an analysis has long been considered to be inappropriate in most epidemiologic applications since it carries the inherent assumption that each exposure increment multiplies the OR by a constant factor (see Greenland 1979, Rothman 1986). Such an assumption is rarely ever appropriate and, in this case, is clearly inconsistent with the leukemia mortality seen in the base population for the case control study (22 observed, 22.8 expected).

Conflict between the cohort and case control study

The lymphopoietic cancer case control study (Matanoski et al. 1989) was nested within the cohort study of 12110 SBR workers (Matanoski et al. 1990). Lymphopoietic cancer mortality for this large cohort was lower than or consistent with general population rates. Specific findings were: all lymphopoietic cancers (55 observed (obs), 56.7 expected (exp), standardized mortality ratio (SMR) = 97), lymphosarcoma (7 obs, 11.5 exp, SMR = 61), and

leukemia (22 obs, 22.8 exp, SMR = 96). Analyses by job category also showed low mortality rates. Importantly, leukemia mortality was not elevated for the two job category subgroups with highest potential for butadiene exposure -- production workers (7 obs, 6.4 exp, SMR = 111) and mechanical workers (6 obs, 8.6 exp, SMR = 70) (corrected figures as in Acquavella 1990).

Against this backdrop, the case control study reported an OR of 7.6 based on the mean of the logarithm of case and control butadiene scores and 60% of the control population was categorized as exposed. Cole demonstrated in his OSHA testimony (Cole 1991) that the case control odds ratio of 7.6 (along with the 60% control exposure prevalence) is incompatible with the lack of any leukemia excess for this worker population (i.e. 22 observed, 22.8 expected). Specifically, he presented the following data:

leukemia deaths predicted in the SBR workers cohort study from the case control results; odds ratio = 8

% cohort exposed	predicted deaths in cohort study
25%	63
50%	103
60%	119

adapted from Cole 1991

As the last row in this table indicates, if the case control OR of 7.6 (Cole used 8.0 for the OR in his testimony) is valid and 60% of the control population is exposed, there should have been 119 leukemia deaths in the cohort study [i.e. (7.6 x 60% of the leukemia expected (22.9)) + (1.0 x (40% x 22.9))] when there were only 22. Allowing for lower exposure prevalences among controls (note the exposure prevalence of controls is representative of the exposure prevalence in the base population conditional on the matching factors - see Miettinen 1985) still yields estimates of leukemia mortality far in excess of that seen in the cohort study. Therefore, until these conflicts between the SBR worker cohort and case control results are resolved, the OR estimates should not be interpreted at face value. Rather, emphasis should be placed on finding an interpretation for the case control results that is consistent with the lack of a leukemia excess for the SBR worker cohort overall.

Checkoway and Williams hematological effects study

CARB mentioned that Checkoway and Williams attributed hematological abnormalities to butadiene exposure in a cohort of SBR workers (Checkoway and Williams 1982). This statement is simply not true since, as Checkoway mentioned, the values for the tank farm workers, the highest exposed group, were all within the normal range. Checkoway and Williams also concluded there was no significant difference between the two exposure groups (i.e. tank farm versus other) in this study. Therefore, CARB's citation of this study is misleading and the conclusion of a relationship

between hematological abnormalities and butadiene exposure is not supported by the available study.

Data on SBR worker subgroups in Matanoski et al. 1990

CARB presented a selected review of the occupational subgroup analyses in the cohort study by Matanoski et al. (1990). Neglected were the findings for white production workers and the data for white and black mechanical workers. These findings are important because process and mechanical workers have frequent opportunity for butadiene exposure according to an industrial hygiene review of the industry (Fajen et al. 1990). The findings

SMRs for mechanical workers by race

	whites			blacks			total		
cause of death	obs	exp	SMR	obs	exp	SMR	obs	exp	SMR
all cancers	173	176.6	98	23	30.8	75	196	207.4	95
all lymphopoietic cancer	14	16.5	85	0	2.1	0	14	18.6	75
lymphosarcoma	2	3.4	59	0	0.3	0	2	3.7	54
leukemia	6	6.4	93	0	0.7	0	6	7.1	85
corrected leukemia*							6	8.6	70
other lymphatic	2	4.4	46	0	0.7	0	2	5.1	39

from Matanoski et al. 1990
* from Acquavella 1990

for mechanical workers (see table above) are particularly important because these workers have had opportunity for intermittent peak exposures and CARB has drawn an analogy between the peak exposure mouse studies (Melnick 1990) and findings from

epidemiologic studies.

From this table, it is obvious that mortality rates for cancers, and specifically lymphopoietic cancers, are not elevated among mechanical workers. SMRs were especially low for the lymphopoietic cancers, specifically: all lymphopoietic cancer SMR = 75, lymphosarcoma SMR = 54, leukemia (corrected) SMR = 70, and other lymphatic cancer SMR = 39. In contrast to the findings reported for black production workers, black maintenance workers had no lymphopoietic cancer deaths (viz. SMRs = 0 for lymphosarcoma, leukemia, and other lymphatic cancer). Therefore, since mechanical workers have intermittent high exposures to butadiene, these data are inconsistent with CARB's analogy to the high exposure/short-time mouse studies by Melnick et al. (1990).

CARB mentions the significantly elevated lymphopoietic cancer mortality and leukemia mortality for black production workers (6 obs SMR = 507, 95% CI 183-1088; 3 observed, SMR = 656, 95% CI 135-1906), but the corresponding lack of lymphopoietic and leukemia excesses among white production workers was not emphasized (13 obs, SMR = 110, 95% CI 58-187; 4 observed, SMR = 84, 95% CI 22-215). Production workers of both races were also reported to have had elevated SMRs for the category "other lymphatic cancers" - a "catch-all" category which includes unspecified non-Hodgkin's lymphoma, multiple myeloma, and

SMRs for production SBR workers by race

	whites			blacks			total		
cause of death	obs	exp	SMR	obs	exp	SMR	obs	exp	SMR
all cancers	105	118.9	88	19	16.5	115	124	135.4	92
all lymphopoietic cancer	13	11.9	110	6	1.2	507	19	13.1	146
lymphosarcoma	0	2.4	0	1	0.2	532	1	2.6	39
leukemia	4	4.8	84	3	0.5	656	7	5.3	134
corrected leukemia*							7	6.3	111
other lymphatic	7	3.1	230	2	0.4	482	9	3.5	260

from Matanoski et al. 1990
* from Acquavella 1990

polycythemia vera. A more appropriate analysis of this data would have shown that there was not an overall lymphoma excess for these workers. Based on data presented by the authors it has been estimated that all lymphoma mortality was consistent with expected values (4 observed, 4.3 expected, SMR = 93, 95% CI 25-238), while multiple myeloma was somewhat elevated (5 observed, 1.7 expected, SMR = 294, 95% CI 95-686) (see Acquavella 1990 for details). This analysis again highlights the inconsistency of lymphopoietic cancer findings across studies.

Studies of Tire Manufacturing Workers

It was mentioned previously to CARB that studies of tire manufacturing populations are essentially irrelevant for butadiene since butadiene in not liberated during tire

manufacturing, and it is not a solvent used in those plants. CARB has chosen to disregard this comment and we state it again for the record. Only one of these studies had a small subcohort of workers employed in the "synthetic plant" where styrene butadiene rubber (SBR) was made at times (McMichael 1976). However, even for these workers, it is unclear whether the synthetic plant resembled production SBR plants (in design and relative production volume), whether there were typical butadiene exposures, and there was acknowledged opportunity for exposure to numerous potential confounding factors in this study (e.g. benzene and other solvent exposure, other elastomeric ingredients). Finally, further studies by this research group attributed the elevated leukemia findings to solvent exposure, not butadiene (See Checkoway 1984). As Matanoski (1990) stated on this issue "In a subsequent study, these investigators associated the leukemia risk with solvent exposure only and did not mention a relationship to the SBR department." (referring to Checkoway 1984). CARB should not confuse the evaluation of butadiene by discussing tire manufacturing studies in detail, but rather should focus on studies of SBR workers and butadiene monomer workers.

Interpretation of findings from Ott et al.

CARB's interpretation of the SB latex workers findings from Ott et al. reflects an unwillingness to accept negative findings from any study. In this study, it is clearly stated that there were no leukemias among 391 SB latex workers. CARB's contention

that this finding is not reliable because "OEHHA staff were not able to confirm that this OTG was the only one in which butadiene exposure occurred" evokes a biased perspective on this study. CARB did not apply an similar concern to the interpretation of the synthetic plant findings in McMichael et al. (1976). However, even if there were other butadiene exposed workers in this study, it would not detract from these SB latex worker findings. They stand as reported.

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OSHA DOCKET NO. H-041

INFORMAL PUBLIC HEARING ON THE PROPOSED OSHA STANDARD ON OCCUPATIONAL EXPOSURE TO 1,3-BUTADIENE

WRITTEN STATEMENT

OF

STUART Z. CAGEN, PH.D.

November 26, 1991

COMMENTS ON NIOSH QUANTITATIVE RISK ASSESSMENT FOR 1,3-BUTADIENE

by

STUART Z. CAGEN[1/]

INTRODUCTION

At the request of the Butadiene Panel of the Chemical Manufacturers Association (CMA), I have reviewed the risk assessment on butadiene prepared by NIOSH (1991). I have been assisted in this review by other members of the CMA Butadiene Toxicology Research Task Group, as well as by other toxicologists and risk assessment experts at Shell Oil Company and other Butadiene Panel member companies. I would like to gratefully acknowledge their assistance.

The NIOSH risk assessment document identifies most of the qualitative and quantitative information that now exists with respect to the carcinogenicity of butadiene. Unfortunately, NIOSH has utilized only a portion of these data for its quantitative risk estimates, and therefore is presenting an incomplete statement regarding risk. It is difficult at this time or perhaps any time to expect risk assessments to have perfect data in the form of directly useable *in vivo* human data. Yet, it is important to use all available information to establish a most likely case and show a range of probable outcomes. The risk manager (OSHA) needs to be informed of this range of probable outcomes, and in order to do this it is important that risk assessments use all of the available information. This is consistent with the objectives of OSHA; the preamble to the proposed butadiene standard (August 10, 1990, 55 FR 32763) states: "When pharmacokinetic or metabolic data are available, these data should be used to estimate internal dose. By using all available information, the uncertainty associated with estimating risks across species can be reduced." We agree with this statement and urge that risk analyses like the one provided by NIOSH utilize as much current metabolic and mechanistic data as possible in order to arrive at estimates of risk to humans.

COMPLEX NATURE OF BUTADIENE RISK OPTIONS: Butadiene presents a challenge to the risk assessor and risk manager because of the numerous choices available from which risk values can be calculated. There are several epidemiology studies as well as three valid rodent bioassays. From the epidemiology side the results are largely negative, although it might be recognized that within the total epidemiology data set there are isolated anomalies that run counter to conventional dose-response principles or are

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statistical artifacts (also see comments of IISRP for more detailed analysis of the NIOSH presentation of epidemiology). In addition, on the surface, there seems to be some confusion regarding the "most appropriate" data set from which risk can be calculated from rodent studies. Clearly, the mouse oncogenicity studies would raise great concern over statistically significant increases in lung tumors at exposure levels as low as 6.25 ppm (NTP-II). Yet there is also a high dose lifetime rat oncogenicity study and extensive mutagenicity and metabolism data on butadiene and related compounds that aid in characterizing the risk. Inclusion of all of the available information in the calculation of risk options is important to the goal of deriving useable and credible values.

SUMMARY OF COMMENTS: We find the NIOSH document to be reasonable in its presentation of most of the pertinent literature relating to the toxicity, carcinogenicity, metabolism and pharmacokinetics of 1,3 butadiene. However, we disagree with the risk assessment approach of NIOSH in utilizing only a small portion of this information in arriving at its calculated workplace risk. Indeed, the analysis presented by NIOSH concludes with a numerical representation of the risk (597/10,000) which might be viewed as an extreme value at one end of a family of estimates. NIOSH has limited the options by rejecting much information and in so doing is giving an incorrect and misleading accounting of likely human cancer risk. Insufficient arguments are given by NIOSH for rejecting the direct use of the rat tumor data and for not using appropriate multi-species pharmacokinetic data to establish a reasonable biological estimate of human risk.

Specific areas covered in detail include:

* NIOSH risk assessment rejected certain data with the implication that the information that does exist is insufficient for any use. These data include:

  Rat oncogenicity study (IISRP).
  Species specific genotoxicity.
  Species specific metabolism.

* NIOSH risk assessment used allometric scaling of body weight to the 0.75 power on the basis of empirical grounds that were derived for compounds other than butadiene. Butadiene specific information should be used, with different results.

* More appropriate treatment of mouse and rat tumor data, including information with regard to metabolism, such as the more reasonable use of internal dose of butadiene epoxide(s) as a dose measure, would significantly reduce the calculated risk.

I. NIOSH RISK ASSESSMENT REJECTED CERTAIN DATA WITH THE IMPLICATION THAT THE INFORMATION THAT DOES EXIST EXIST IS INSUFFICIENT FOR ANY USE

A. Rat Oncogenicity Study (IISRP)

Although the NIOSH risk assessment did not explain in great detail NIOSH's reasons for rejecting the rat oncogenicity study, there were three identifiable comments which seem to indicate that NIOSH considered the study as not useful:

> On page 7 NIOSH states that: ". . . Although the study was completed in 1981, it was not formally reported until six years later (Owen, et al, 1987) . . .."
>
> On pages 12-13 NIOSH states (albeit with respect the EPA rejection of the rat study): ". . . the study (at that time) had not been peer-reviewed or published, lacked complete pathology information, allowed larger contaminant concentrations of dimerized butadiene than the mouse study, and exposed rats to concentrations greater than that producing metabolic saturation . . .."
>
> On page 17 NIOSH states that: ". . . This data set is preferable to either the Hazleton rat bioassay data (Owen, et al, 1987), or the first (high dose) mouse bioassay (NTP, 1984), because the new data set includes exposures at a concentration (6.25 ppm) close to the proposed OSHA standard of 2 ppm. The fact that the 1984 NTP data included very high exposure concentrations leads to difficulties in extrapolating the effects to low concentrations since the biologically effective doses were probably not directly proportional to the ppm exposure concentration due to metabolic saturation and possible depletion of glutathione . . .."

These reasons are insufficient justification for using only the new tumor data in mice for calculation of cancer risk. Indeed, the more recent NTP sponsored bioassay has not been peer reviewed, and should be the data set most vulnerable on grounds of insufficient review. The IISRP rat oncogenicity study has been peer reviewed and published and is considered to be a valid bioassay. For further clarification of methodological issues relating to this study (including a description of the procedures used for controlling concentrations of dimerized butadiene, which procedures were clearly more effective than those employed in the NTP-I mouse study) please review the testimony of Dr. Robert Hinderer.

Note also that in its justification of the preferred data set from the new mouse study, NIOSH (on page 17) emphasizes that: "biologically effective" doses were disproportionate in the earlier high dose mouse and rat studies. Although it might be reasonable to prefer the new mouse study to the old one, the results in rats

still provide valuable information, even preferable information, particularly because metabolism of 1,3 butadiene to active metabolites in humans (in vitro) and nonhuman primates (in vitro and in vivo) is much more like rats than mice (also see below). Clearly, if the issue NIOSH wished to pursue (on page 17) was the matching of reasonable "biologically effective" doses, then rat tumor data would be the most appropriate of the available data.

The NIOSH risk assessment, on page 46, summarizes the results of their assessment and compares the results to the prior OSHA assessment. In the end, the NIOSH value is within a factor of two (when an adjustment is made to allow for comparable scaling procedures) of the "high dose" mouse study (NTP-I). Although this result might illustrate limitations in existing extrapolation methodologies, it nonetheless demonstrates (with life shortening adjustments) for butadiene that there is no advantage of having a study with doses "close to the proposed OSHA standard of 2 ppm". The primary issue is the appropriateness of the species being modeled, not the dose. Although corrections need to be made to account for known species differences in metabolism of butadiene (see below), useable and equally valid risk values for mice could have been derived from the high dose mouse study - NTP-I. In a similar sense, the IISRP sponsored rat bioassay cannot be ignored on the grounds that the doses used were too distant from the proposed standard. At a minimum, this dichotomous species response -- high dose mouse yields large tumor response while higher dose rat yields a small tumor response -- must be fully included in a scientifically based risk assessment. Indeed, the rat study should get preference because, as discussed below, butadiene metabolism in humans more closely resembles the metabolism profile in rats as compared to mice.

B. Species Specific Genotoxicity

On page 11: NIOSH gives only a brief accounting of the current evidence for genotoxicity. Although this particular information does not have direct bearing on the final risk calculations, important species differences in the genotoxicity of 1,3 butadiene should be reviewed. It is suggested that the testimony submitted by Dr. Michael Bird be reviewed. The evidence supports the notion that mice are much more susceptible than any other species to genotoxic events produced by 1,3 butadiene either in vitro or in vivo. A more balanced presentation would illustrate to the risk manager (OSHA) that mice are extraordinarily susceptible to genotoxic events produced by 1,3-butadiene, and therefore risk estimates based exclusively on the mouse tumor response would overstate the true risks (also see below).

C. Species Specific Metabolism

As is freely acknowledged by NIOSH, and emphasized extensively by CMA (see testimony of Dr. Michael Bird), the mouse is extraordinary in its ability to produce and retain toxic epoxide metabolites of butadiene. It is commendable that NIOSH fully

captured much of the latest literature in this regard (Kreuzer, et al, 1991; Dahl, et al 1991; Csanady and Bond, 1991). However, it is important that this information also is captured in the quantitative treatment of the tumor and subsequent risk data. Although the optimal situation would be to have all required information available prior to conducting formal risk analyses, this is seldom the case, and it is often necessary to use whatever information is currently present. In a qualitative sense this is in agreement with OSHA (see preamble to proposed standard, August 10, 1990, 55 FR 32763) and NIOSH (page 17; NIOSH, 1991; "biologically effective doses"). These clear qualitative factors should be translated into reasonable species extrapolations acknowledging that the mouse is several times (perhaps several orders of magnitude) more sensitive than other species, including humans. It is recommended that the pre-hearing comments submitted by Shell Oil Company and ENVIRON (on behalf of the CMA Butadiene Panel) be reviewed and considered; these include incorporation of metabolism information into the risk analysis.

Even if the available metabolism data do not permit a complete pharmacokinetics treatment of the data for risk estimation, the available information is substantial enough for guiding the choice of species to be modeled for estimating human risk. The latest in vitro data, which were derived with several human tissue samples, indicate that the rat is the better species to model.

II. NIOSH RISK ASSESSMENT USED ALLOMETRIC SCALING OF BODY WEIGHT TO THE 0.75 POWER ON THE BASIS OF EMPIRICAL GROUNDS THAT WERE DERIVED FOR COMPOUNDS OTHER THAN BUTADIENE. BUTADIENE SPECIFIC INFORMATION SHOULD BE USED, WITH DIFFERENT RESULTS

In justifying the application of 0.75 scaling, the NIOSH risk assessment (on pages 24, and again on pages 47 - 49) references several rather generic papers that deal with this topic (O'Flaherty, 1989; Travis et al, 1990; Travis and White, 1988). Although these papers are based on a reasonable treatment of the data base those authors selected, alternative analyses can also be presented. An EPA sponsored report (INVESTIGATION OF CANCER RISK ASSESSMENT METHODS by Clement Associates for the EPA, 1987; EPA/600/6-87/007d) [copy attached] makes quantitative comparisons of carcinogenic potency in animals and humans for 23 chemicals for which suitable animal and human data exist. One conclusion of the study was: ". . . use of mg intake/kg body weight/day method for animal-to-human extrapolation generally causes risk related doses (RRDs) estimated from animal and human data to correspond more closely than other methods evaluated . . .. " (also see Allen, B.C., Crump, K.S. and Shipp, A.M. Risk Analysis 8(4):531-544, 1988 [copy attached]; and Goodman, G., and Wilson, R. Environmental Health Perspectives 94:195-218, 1991) [copy attached].

More importantly, when considering butadiene, NIOSH does not even respond to their own calculation of a contradiction to the allometric scaling approach. On page 49, the document reviews the apparent inconsistency of 0.75 scaling when rat/mouse kinetic constants for butadiene and the monoepoxide metabolite of butadiene are scaled together (referencing data of Kreiling). This implies that 0.75 scaling is NOT appropriate with respect to butadiene. Further, it is clear that, with respect to mice and rat, the scaling should go in the exact opposite direction.

Further, the argument presented by NIOSH with regard to in vitro data, on page 48, would also support mg/kg scaling (at least), especially with regard to mouse data. Here NIOSH reviews the data of Csanady and Bond where it has been shown that tissues derived from the mouse produce 5-6 times more monoepoxide in vitro than tissues from humans. This would make the mouse MORE susceptible not less, as would be required to justify scaling to the 0.75 power. Moreover, recent data of Csanady and Bond (CIIT Activities, Volume 11 No.2, February 1991) show also that human tissues can detoxify the butadiene monoepoxide nearly 20 times faster than the tissues derived from the mouse. These data are clear and supportive of prior work (see below) in illustrating the extraordinary capacity for the mouse to produce and retain the toxic monoepoxide metabolite(s). The kinetics of these results do not even support mouse to human scaling on a straight mg/kg body weight basis, much less on a 0.75 power factor basis.

If 0.75 scaling were appropriate the implication would be that the larger species (man, rat) would be more sensitive on a mg/kg basis to butadiene that the mouse. This is clearly not the case when examining any of the existing data on butadiene. The clear evidence - be it metabolism data or tumor data directly - is that the mouse is the most sensitive species tested. It is noteworthy that the papers cited above and by NIOSH (that is: O'Flaherty, 1989; Travis and White, 1988) state clearly that compound specific data is preferred:

> O'Flaherty: page 597: ". . . IN THE ABSENCE OF SPECIFIC INFORMATION BEARING ON THE METABOLISM AND TOXICITY OF THE CHEMICAL, the 0.75 power of body weight dose conversion is a reasonable approach . . .. "
>
> Travis and White: page 124: ". . . The National Academy of Sciences and Anderson point out that scaling should depend on the kinetic behavior of the particular compound and mechanism of toxicity . . . the 3/4 [0.75] power may be the most appropriate interspecies scaling factor for use in risk assessment of DIRECT ACTING COMPOUNDS. Further analysis will be needed to determine the appropriate scaling factors for compounds that are activated by metabolism."

Considering what is now known about the toxicity and metabolism of butadiene in a variety of species, it is imperative to use the compound specific information to arrive at the most scientifically based scaling factor when extrapolating to humans. For example, because it is universally accepted that epoxide metabolite(s) are the "direct acting" toxicants, scaling based on a 3/4 power of body weight might be used only after adjustments are made to account for species differences in the formation and de-activation of these toxic metabolites.

Species specific metabolism data (please review prior testimony of Dr. Michael Bird and below) clearly show the unique properties of the mouse with respect to activation of butadiene to toxic metabolites as well as deactivation of these epoxides to less toxicologically important moieties. A similar trend in results of toxicology results should also not be ignored. As a simple example, one can look at the data from the risk assessment prepared by the EPA in 1985 (USEPA: Mutagenicity and Carcinogenicity Assessment of 1,3 Butadiene, August 1985). The EPA calculated that the risk estimate (unit cancer risk) from the female and male mouse is about 8 or 200 times higher than those corresponding to the female or male rat, respectively. Scaling the mouse data using 0.75 scaling to predict a rat risk would go in the exact opposite direction. Thus, with respect to the experimental toxicology findings, the 0.75 scaling assumption clearly is not valid.

III. MORE APPROPRIATE TREATMENT OF MOUSE AND RAT TUMOR DATA, INCLUDING INFORMATION WITH REGARD TO METABOLISM (I.E., THE MORE REASONABLE USE OF INTERNAL DOSE OF BUTADIENE EPOXIDE(S) AS A DOSE MEASURE), WOULD SIGNIFICANTLY REDUCE THE CALCULATED RISK.

A. Comment On The Discarding Of Data By NIOSH

The NIOSH risk assessment states (on page 20): "Exposure concentration was chosen in preference to measures of internal dose, such as butadiene concentration or butadiene monoepoxide concentration, due to the lack of reliable measurements of these concentrations in mice, and the absence of any measurements in humans." On pages 52 and 53, the document goes on to justify this decision in light of an apparent inconsistency of Bond data to those of Kreiling and the difficulty of NIOSH in accepting data of Dahl and Bond because the cyrogenic trapping method might be too nonspecific. In addition, the NIOSH risk assessment, on pages 5 and 6, is critical of studies of Bond, et al (1986) and Dahl, et al (1990, 1991) because of apparent inconsistencies (blood butadiene levels higher at 2 and 4 hours in 7 ppm exposed mice than in 70 ppm exposed mice) or difficulties in relating 2 hour anesthetized monkey data to 6 hour unanesthetized rodent data.

In developing the argument regarding the cyrogenic trapping procedure of Dahl and Bond, NIOSH suggests that the method "might not distinguish 1,3 butadiene from other 1,3 butadiene metabolites." Indeed, even if this were to be a valid point, the results of Dahl are still useable in that the higher blood levels of 1,3 butadiene monoepoxide or "other metabolites" in the mouse over the rat and primate still implies that the production and retention of monoepoxide and other metabolites are much higher in mice. Since it is universally accepted that all metabolism of 1,3 butadiene MUST begin with the production of the first monoepoxide, it might matter little whether those blood levels represent monoepoxide or subsequent (similarly volatile) metabolites. Other issues raised by NIOSH -- those of rather minor inconsistencies in specific data sets, or the relative importance of anesthesia on butadiene metabolism, are addressed in the post-hearing testimony of Dr. Michael Bird. Most importantly, it must be remembered that the data set AS A WHOLE is internally consistent.

In particular: in vitro metabolism, in vivo metabolism in several laboratories (those of Kreiling, Bolt, Dahl, Bond, and all of their co-workers), and data concerning genotoxicity and carcinogenicity clearly set the mouse apart as a species extraordinarily sensitive to the toxicity of butadiene because of an extraordinary capacity to produce and maintain toxic epoxide metabolite(s). TABLE 1 (attached) summarizes a portion of the existing metabolism data base.

B. Use Of Physiologically-Based Pharmacokinetics

On page 5 of their risk assessment, NIOSH is critical of the direct use of the Bond data to estimate retention of butadiene because no attempt was made to estimate the extent to which butadiene metabolites were excreted in the breath during the six hour exposures. Although the NIOSH-sponsored study of Hattis and Wasson addressed this very point, on page 15 of the NIOSH assessment, NIOSH claims that not enough validation has been performed to warrant direct use of the results. Nonetheless, the Hattis and Wasson report concluded (among other things) that human absorption and metabolite formation at low doses is much lower than assumed by EPA (in their prior risk assessment). The Hattis and Wasson study concluded that there was an underestimation of actual dose received by mice and rats by factors of 2 and 4.5, respectively; this would result in a reduction in calculated risk.

C. Adjustments To Risk Values According To Known Differences In Butadiene Metabolism Across Species

Because of the significant amount of information now available from multiple laboratories concerning species differences in the metabolism and toxicity of butadiene, it is appropriate to utilize this information and incorporate these factors into the selection of the species to model and the calculation of risk. Although the NIOSH risk assessment mentions many of these results

the only one that is used to calculate risk is the second mouse oncogenicity study (NTP-II).

It is possible to make all of the data more compatible by demonstrating that adjusted risk values reduce the rat/mouse differences. The adjustment factors, derived from the metabolism/pharmacokinetics data base, explain in a quantitative way why the mouse would be expected to be more vulnerable than any other species, including man. One demonstration of the use of these adjustment factors has been submitted by Shell Oil Company and it is recommended that their risk assessment be reviewed. It is also recommended that the pre-hearing comments regarding the quantitative treatment of risk by ENVIRON also be reviewed.

A demonstration (used here as an example) of this can be made here:

	RAW POTENCY (unadjusted) (2 ppm)	ADJUSTMENT[2/] METABOLISM (epoxide)
NIOSH MOUSE (FEMALE)	5.97/100	0.1/1000
OSHA RAT (FEMALE)	0.29/100	0.07/1000

D. Comments By ENVIRON On The NIOSH Risk Assessment

Additional comments on the NIOSH risk assessment have been prepared by ENVIRON (on behalf of CMA). These comments illustrate quantitatively the impact of NIOSH's choice of the external concentration of butadiene as the measure of delivered dose on the estimate of risk. A table is presented to illustrate the impact on the NIOSH risk estimate if data on uptake, retention and metabolism are used as the basis for a more scientifically supportable measure of delivered dose. The approaches urged by ENVIRON produce a more plausible range of likely cancer risks. ENVIRON also illustrates the inconsistency between the NIOSH estimate of risk and the results of epidemiology studies.

2/ Adjustment to account for differences in the production of the butadiene monoepoxide in blood: factors of 590 in mice and 40 in rats (from Dahl, et al, 1990 using primate data).

CONCLUSION

In conclusion, we would like to reiterate the following key points with respect to the NIOSH risk assessment.

1. Generically risk assessments can and should use all of the available information to establish a most likely estimate along with a range of possible outcomes. Perfection of data need not be a prerequisite to using it.

2. For butadiene, this includes recognizing the marked species difference in tumor response between rats and mice, and the large body of comparative metabolism, pharmacokinetics, and genotoxicity data which includes studies using non-human primates and human tissue. These data consistently indicate the B6C3F1 mouse to be a uniquely susceptible species and the rat as a preferable model for extrapolation to humans.

3. NIOSH has chosen to essentially ignore this substantial database in favor of generic, default assumptions. This approach has lead to a particularly conservative risk assessment which is inconsistent with the available evidence (including worker mortality experience) and may be properly viewed as the conservative end of a range of possible risk estimates. A more credible risk assessment would account for the available butadiene-specific data (e.g., rat bioassay, internal dose, etc.).

4. The approximate order of magnitude difference between the NIOSH and OSHA risk assessments is <u>not</u> primarily due to the more recent dose-response data from NTP II. Rather, it is due primarily to NIOSH's chosen methodology, particularly their decision to scale using body weight to the 0.75 power.

5. NIOSH's scaling assumption is improper because 1) compound-specific data, when available, is preferable and 2) available butadiene-specific data are inconsistent with this scaling assumption (e.g., it predicts the rat would be more sensitive than the mouse).

For these and other reasons expressed in these comments, we believe the NIOSH risk assessment document overstates the likely human cancer risks from workplace exposure to butadiene.

TABLE 1

KNOWN SPECIES DIFFERENCES IN THE METABOLISM OF 1,3 BUTADIENE

AUTHOR(S)	STUDY TYPE	SPECIES MOUSE	COMPARISONS RATS	PRIMATE	AMOUNT THE MOUSE IS MOST SENSITIVE*
KREILING	IN VIVO	X	X		10
SCHMIDT/LOES	IN VITRO	X	X	X (MAN)	60
CSANADY/BOND	IN VITRO	X	X	X (MAN)	60
DAHL	IN VIVO	X	X	X	590

* = Based on the data in the study, the value represents the magnitude of measured difference in the amount of toxic epoxide metabolite(s) present in the mouse, when compared to other species. The in vitro data of Schmidt and Loeser as well as of Csanady and Bond are calculated based on the 3-fold greater activity of the mouse to produce the monoepoxide metabolite and a 20-fold greater activity of the human to detoxify this metabolite (3 X 20 = 60).

Because these were obtained from differing experimental situations, the numerical values would not be expected to be the same. Nonetheless, all of the values clearly show that the mouse produces and retains reactive epoxide metabolite(s) greater than other species. Of the data shown, the results of Dahl should be considered to be the most directly useable for risk assessment purposes because less extrapolation is needed from the experimental setting.

CURRICULUM VITAE

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1971-1973 Quality Control Laboratories, Pabst Brewing Company, Milwaukee, Wisconsin

1973-1977 Predoctoral Fellow, Michigan State University, Department of Pharmacology, East Lansing, Michigan

1977-1979 Postdoctoral Fellow, University of Kansas Medical Center, Kansas City, Kansas

1979-1980 Research Scientist-Toxicologist, Basic Research Department, Frito-Lay, Inc., Irving, Texas

1980-1986 Research Toxicologist, Shell Development Co., Houston, Texas

1986- Senior Toxicologist, Shell Oil Company, Houston, Texas

1990-present Shell representative to CMA Butadiene TRTG*

1984-present Products/Process Toxicologist for Catalysts

1984-present Shell representative: Chemical Manufacturers Association (CMA) Special Panel on Metal Containing Catalysts
Panel Vice-Chairman (1988)
Chairman, Toxicology Task Group (1984-)

1984- Shell Oil Co., Risk Evaluation Group, Toxicology representative to risk evaluation committee

HONORS: Eli Lilly Fellowship Award (1975-1977)
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UNIVERSITY ACTIVITIES:

1972-1973 University of Wisconsin, Senior Thesis Research

1975 Michigan State University, Lecturer in Pharmacology

1974-76 Participant in Michigan State University, University of Michigan, Wayne State University, Medical College of Ohio at Toledo, Annual Pharmacology Research Colloquium

1977 Lecturer in Readings in Toxicology, University of Kansas Medical Center

NATIONAL ACTIVITIES:

Contributor to Symposium, Biochemical Mechanisms of Paraquat Toxicity, The University of Iowa, June, 1976.

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Contributor to Second International Biological Reactive Intermediate Meeting, Guilford, England, July 1980.

Lecture in Industrial Toxicology in Practical Toxicology Principles, The Center for Professional Advancement, Houston, Texas, March 1981.

Guest Lectures at: The Medical College of Wisconsin, University of Texas Health Science Center-Dallas, University of Texas Health Science Center-Houston, Northwestern Medical Center, The Upjohn Company.

Member 1982-1983, Society of Toxicology Technical Committee

Member, 1987-1988, American Industrial Health Council, Neurotoxicology Subcommittee

Co-organizer/Founder, Society of Toxicology, Gulf Coast Chapter; Sec/Tres 1983-1985.

Co-organizer/Founder, Society for Risk Analysis Lone Star Chapter; Tres. 1988.

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INFORMAL PUBLIC HEARING ON THE PROPOSED OSHA STANDARD ON OCCUPATIONAL EXPOSURE TO 1,3-BUTADIENE

SUPPLEMENTAL TESTIMONY

OF

MICHAEL G. BIRD, PH.D.

November 26, 1991

POST HEARING SUPPLEMENTAL STATEMENT OF DR. MICHAEL BIRD ON KEY INTERSPECIES DIFFERENCES IN METABOLISM AND CYTOGENICITY OF 1,3-BUTADIENE

My name is Dr. Michael Bird, and I submit this post-hearing statement on behalf of the 1,3-Butadiene Panel of the Chemical Manufacturers Association. This statement supplements my previous written testimony as well as my oral testimony at the hearings on January 18, 1991 in Washington, DC. I take this opportunity to focus on points asked of me and others, by the OSHA Panel relating particularly to the interspecies differences in the pharmacokinetics and metabolism of 1,3-butadiene. However, key new data introduced at the OSHA hearings and in subsequent scientific publications support and further define the position I presented from two of the three endpoints I discussed, metabolism and cytogenetics.

My testimony showed that there are major quantitative differences between species in the formation and clearance of the reactive metabolites of butadiene and that on this basis, the mouse would be an overly sensitive model for man. New data (Csanady and Bond, 1991) indicate that the key difference in metabolism between rodent and man is the predominant and rapid metabolism of butadiene monoepoxide by epoxide hydrolase in man to non-DNA reactive 1,2-dihydroxy but-3-ene; this is in contrast to the slower but major contribution of the cytochrome P-450 in the mouse to metabolize the monoepoxide to a DNA-reactive and cross linking agent, the butadiene diepoxide. The urinary metabolite profiles for mouse and primate also reflect this difference (Henderson unpublished, Sabourin, et al. 1990). Ki-ras oncogene activation and/or MULV retrovirus activation appear as secondary to the initiating effects of the circulating mono- and diepoxides in the mouse. Perhaps linked to this is the new finding that like the rat,

micronuclei or chromosomal changes are not present in primates exposed to 8,000 ppm butadiene for up to two hours. These changes are seen in the mouse and possibly the hamster.

These and other data to be discussed subsequently continue to show that because of species differences in metabolism, a carcinogenic response in humans would not be expected to occur at current occupational exposures (10 ppm TWA or less).

Supplemental Answers to Questions Raised During Cross-Examination:

1. Data Derived from Primates

Primates are preferred in advanced pharmacokinetic and toxicokinetic studies because enzyme profiles and metabolic capacities are similar to human and because anatomical and physiological parameters (respiratory rate, blood flow) are more closely matched. Examples of the use of primates as models in pharmacological and toxicological testing are given in Table I. Primates would be used even more extensively but for limitations in availability, difficulties in handling and animal rights considerations.

Within primates, there are examples of metabolic pathways not replicated in other members including man. For example, a Cercopithecus species monkey converts endogenous purines to allantoin and not to uric acid as occurs in the chimpanzee and man. The metabolic reactions in the Rhesus and the cynomolgus monkeys have been

determined and include, as is the case for man, the Phase I (oxidative, reductive and hydrolytic) and Phase II (synthetic) reactions known to be involved in butadiene metabolism.

As a general comment, there are some metabolic reactions which are restricted in their occurrences to primates and hence the appropriate model for man should be sought from anthropoid or promazine species. One example of a pathway present in man and in primate but not in nonprimate mammals is that of conjugation by glutamine rather than glycine for acetoacetic acids such as phenylacetic acid. For a meaningful metabolic comparison, not only is the pathway to be similar but so too should the rate of metabolism. In this respect, the monkey has a similar rate of metabolism to man for plasma half-lives of xenobiotics of less than 30 hours (as is the case of butadiene and its epoxide metabolites).

In vivo inhalation studies in the primate by Dahl, et al. (1990 and 1991) show similar qualitative and quantitative production of reactive epoxide metabolites of butadiene as found in in vitro primate and human tissue preparations (Schmidt and Loeser 1985; Kreuzer, et al. 1991), but different from mouse (Bond, et al. 1986). The same is true for urinary metabolite data (Sabourin, 1990; Henderson 1991 unpublished) where the absence of a metabolite II mercapturic acid of butadiene epoxide in the primate, but its presence in the mouse, indicates a detoxification pathway in the primate which is not utilized in the mouse.

The above generic examples of the use of the primate and the specific data for butadiene metabolism indicate that the primate is an acceptable model for man.

2. Anesthesia/Respiration Rate

The studies of Dahl, et al. (1990 and 1991) used a light anesthesia of ketamine/halothane and subsequently pentobarbital during the experimental period. Respiration data including breathing frequency and tidal volumes during exposure were determined. It was from these data and from the knowledge of the minute volume of the resting, unexposed cynomolgus monkey (obtained from ITRI, Lovelace) that the 15-20% percent reduction due to anesthesia was calculated and mentioned in my oral testimony. Dr. Henderson (1991) states that the effects of this anesthesia in dogs results in a decrease in minute volumes of about 25%. She notes that the same or similar changes for the monkey could not account for the 4-10 fold lower uptake of butadiene in the monkey compared to the rodent.

Of additional note is the observation from data of Dahl, et al. (in press) that a 2 hour exposure of the primate to 8000 ppm butadiene decreased the minute volume significantly in comparison to comparable exposures of 310 ppm and 10 ppm. This demonstrates that the anesthesia used is light enough so as not to mask the CNS depressive effects of butadiene on respiration anticipated at such high exposures.

3. 2 Hour Exposure for the Primate

Dr. Henderson's team (which conducted the primate and rodent studies) confirm in their post hearing comment (Henderson 1991) that a 2 hour period is sufficient to obtain steady state for the blood in any species if not for fat retention. My examination of the mouse and rat data from Bond, et al. (1986), specifically of the quantitative levels of volatile metabolites at 2, 4, and 6 hours, showed that the concentration of any specific metabolite was similar across the time points (within experimental variation), indicating that near steady state had been achieved by 2 hours. Although not stated, in Table 6 of the Dahl paper (1991), the data from the 2 hour (not 6 hour) time points of Bond, et al. (1986) are used in comparison with the 2 hour primate data, thus providing comparability.

4. Normalization of Total Uptake

It might be expected that the ratio of species differences in metabolites distilled from the blood (Dahl, et al. 1991) would not be maintained when normalized for total uptake since elsewhere (Table 5) in this paper data show that the blood of mouse and rat contain more free butadiene than the primate. This may be partly due to the greater uptake of butadiene in the rodent, but also the primate and to a lesser extent the rat, have carbon dioxide as an excretory pathway which does not occur to the same extent in the mouse. Hence, the free butadiene in the blood of the rodent is available for metabolism to reactive metabolites, which means that the total uptake divisor is larger in these rodents because of the free butadiene. This results in apparently lower proportional metabolite concentrations and

consequently reduces or reverses the ratio of metabolites across species. Hence, I believe the ratio and the supporting data are consistent with marked interspecies differences and with the greater formation of reactive epoxide metabolites in the mouse compared to rat or to primate.

5. Enzyme Induction

Studies by Bond, et al. 1988 (also Dahl, et al. 1990) report that repeated exposure does not induce metabolism of butadiene in rodents. As is the case for butadiene dimer (Smith, et al. 1990), it is believed that the metabolism of butadiene is through cytochrome P-450IIE. Styrene amongst others, is known to be metabolized through cytochrome P-450IIE (Guengerich, et al. 1991) and would, therefore, be a competitive substrate for butadiene upon coexposure. There is some evidence (Dahl, et al. 1990) to suggest that like propylene, butadiene may deactivate cytochrome P-450 and partially inhibit its metabolism. The kinetics and possible induction by butadiene of epoxide hydrolase and of glutathione conjugation (both detoxification pathways) is being examined at ITRI Lovelace in research sponsored by the CMA Butadiene Panel.

6. Lorenz Data

These data (Lorenz, et al. 1984) show interspecies differences in specific enzymes in subcellular preparations of rodent and human lung and liver exposed to 1-chloro 2,4 dinitrobenzene (not butadiene or its

metabolites). While specific enzyme activities can vary accordingly to substrate, the ratios derived from the Lorenz data that I presented in my testimony are largely consistent with the interspecies differences in cytochrome P-450 and epoxide hydrolase activities described in in vitro studies for mouse, rat, primate, and man by Schmidt and Loeser (1985). More extensive work by the Chemical Industry Institute of Toxicology (Csanady and Bond 1991) is defining better the complexities of the in vitro system with the conclusions that the mouse retains significantly more of the epoxide once formed than man.

7) Human Variability/Sample Size

A reasonable criticism of the human metabolism data for butadiene has been its dependence on limited samples (in each case one human subject for Schmidt and Loeser [1985] and Kreuzer, et al. [1991]). Wistuba, et al. (1989) report that the differences in optical isomers of aliphatic alkene epoxidation by human liver microsomes of four individuals were negligible, but the optical isomers of the butadiene monoepoxide in man were more similar to the mouse than to the rat. While there is no information available as to the relationship of the optical isomeric "R" and "S" forms to their ability to be formed through isozyme activity, kinetic studies in human, mouse, and rat tissues have been conducted by Csanady and Bond (1991). These in vitro studies show a greater formation of butadiene monoepoxide formation in the mouse than man, and once formed, the monoepoxide in man is quickly detoxified with negligible formation of the diepoxide; in mouse the monoepoxide remains longer while being in part metabolized to the

reactive diepoxide. This is consistent with the finding of significantly higher circulating blood levels of mono and diepoxide in the mouse compared to that of primates when similarly exposed to 1,3-butadiene (Dahl, et al. 1990). To minimize any inter-individual variability in isozymes, detailed kinetic studies using human liver and lung tissues from 12 humans are being completed at CIIT (Csanady) and at the GSF-Institute for Toxicology (Kreuzer).

8) Epoxybutene Metabolism

Data from Bond, et al. (1986) show that epoxybutene metabolism in the mouse becomes saturated at 500 ppm and that the mouse is unable to remove this active metabolite. While saturation levels may not be reached in practice, species differences in the rate of expoxybutene metabolism are important at exposures lower than 500 ppm. Csanady and Bond (1991) show that human liver tissue metabolizes epoxybutene significantly faster than mouse or rat forming the non DNA-reactive 1,2-dihydroxy-3-butene. Clearance in the mouse of the reactive epoxybutene takes longer, and when it occurs, produces the butadiene diepoxide and the 1,2 dihydroxybut-3-ene.

9) Oncogenes

The exact role of oncogenes in malignancy is unknown, but studies by Leigh, et al. (1990) indicate that at least for the Ki-ras oncogene, this occurs later in the transformation process. In order to become activated to a transforming gene, a genetic event has to occur; for ras

oncogenes this can be a point mutation or an overexpression or amplification. Either event could be initiated by a reactive metabolite such as the diepoxide of butadiene which can form cross links with DNA. Hence, I see Ki-ras oncogene as a part of the mechanism for the observed cancer and not the cause, and its activation as being entirely consistent with the presence of DNA-reactive metabolites in the mouse.

10) Pharmacokinetic Data on 4-Vinylcyclohexene (VCH)

The species differences in pharmacokinetics and metabolism of 4-vinylcyclohexene (butadiene dimer) have been described in pages 36-39 of my previous testimony to these OSHA hearings. There is close analogy between VCH and butadiene metabolism and demonstrable species differences between the mouse and the rat as the mouse has a greater capacity than the rat to convert the parent VCH to reactive intermediates. Intraperitoneal injection (800 mg/Kg) of VCH resulted in 41 nmol/ml of the monoepoxide (VCH - 1,2-epoxide) in the blood of mice 2 hours after injection, whereas the blood concentration of VCH-1,2-epoxide was less than 2.5 nmol/ml for the rat (Smith, et al. 1990a).

In vitro studies (Smith, et al. 1990b) showed a 6.5-fold greater rate of epoxidation in the mouse liver than that in rat liver microsomes. In further studies, these authors associated the VCH epoxidation with certain cytochrome P-450 isozymes and went on to show that, although cytochrome P-450IIB catalyses VCH epoxidation in both

cytochrome P-450IIB in rats than mice per amount of protein. The lower concentration of cytochrome P-450IIB in the female rat is, at least, partially responsible for the lower rate of VCH epoxidation in the rat and may well be the explanation for the lack of ovarian toxicity in female rats exposed to VCH.

Recently, Smith and Sipes (1991) assessed the ability of microsomes obtained from human liver to metabolize VCH to epoxides. VCH-1,2-epoxide was the major metabolite, while the rate of VCH-7,8-epoxide formation was about 6-fold lower, and in some cases, was below the limit of detection. There was no dramatic difference in the rate of VCH epoxidation obtained from male and female humans. However, the rate of VCH-1,2-epoxide formation by female human hepatic microsomes was 13- and 2-fold lower than the rate of VCH-1,2-epoxide by female mouse and rat hepatic microsomes, respectively. Hence, as cytochrome P-450IIA and cytochrome P-450IIB account for the majority of VCH bioactivation in the mouse liver, and these isozymes are present to a lesser extent in the rat, then the results of these studies suggest again that rats are the more appropriate animal model for extrapolation of animal data to humans for butadiene dimer and for 1,3-butadiene.

New Data Demonstrating Species Differences:

In addition to the above new data by Smith and Sipes, others (Bond and Csanady 1991) have provided further in vitro data supporting the species differences in metabolism of butadiene and of butadiene monoepoxide in both the liver and lung of the $B_6C_3F_1$ mouse, Sprague Dawley rat, and the human.

Using samples from 12 different human livers, they report that butadiene metabolism as represented by V_{max}/Km ratio is about 6 times higher in mice than in humans or rats and that the subsequent removal of the mutagenic epoxide is 4 fold more rapid in the human than in the rodents. For the human, this removal represents the conversion to inactive 1,2 dihydroxbut-3-ene while in the mouse, the active butadiene diepoxide is formed as well.

Bond and Csanady also reported that the metabolic contribution of human lung microsomes in the metabolism of butadiene is negligible. In the mouse lung, significant metabolism of butadiene monoepoxide occurs. Their interpretation of these data is that differences in the rates of metabolic activation of butadiene in target tissues may be a critical factor in tissue and species sensitivity to butadiene carcinogenesis. An abstract describing their further studies to substantiate and extend these findings has been accepted for presentation at the Society of Toxicology Annual Meeting, February 1992.

Other in vitro data have become available from the Inhalation Toxicology Research Institute in Albuquerque, New Mexico. The data are from a preliminary report (ITRI 1991), an initial phase of the Chemical Manufacturers Association Research Program on Butadiene. Total butadiene metabolism was measured in microsomal preparations from liver and lung samples from humans and mice. Higher butadiene metabolism was found in mouse liver than in human liver; the ratio of activity in the mouse liver compared to human liver is consistent with that reported by Schmidt and Loeser (1986).

The Chemical Manufacturers Association, in conjunction with the American

Petroleum Institute, has begun a four year research program to increase the understanding of the mechanism of action and species differences in response. Four research centers with extensive previous involvement and expertise in butadiene research are involved. At the Inhalation Toxicology Research Institute, the original interspecies studies at this Institute (Bond, et al., 1986; 1988 and Dahl, et al. 1990; 1991) are being extended to include determinations across species of tissues and blood after both single and repeated exposures of butadiene to rodents and primates. Such studies will augment the available internal dose data for risk assessment.

Other data from this Institute (Dahl personal communication) shows the lack of micronuclei induction or chromosome effects in the blood of primates immediately following or 3 days after a 2 hour exposure to 8,000 ppm butadiene; this is in contrast to the significant response seen in the mouse under similar exposure conditions. The University of Colorado's part of the CMA program is aimed at understanding the marked species differences in susceptibility leukemia. Comparative studies are characterizing the cell-specific metabolism and fate of butadiene metabolites in purified lines of mouse and human bone marrow stem cells. The University of North Carolina is identifying and measuring any specific mutations that occur in mouse, rat and human cells in culture and will assess the significance of such changes.

The Chemical Industry Institute of Toxicology (CIIT) is generating a physiologically-based pharmacokinetic model to improve the prediction of cancer risk and which will incorporate much of the data being generated both at CIIT and at the other centers. Specific details of this ongoing program are contained in an abstract (Bird, et al.) presented at the International

Symposium on the Health Effects of Gasoline in November 1991 at Miami, Florida. While data from this program are preliminary, the initial work to date using these various approaches/end points continues to show that the sensitivity of the mouse to butadiene is in large part due to that species particular metabolism.

Since the OSHA hearings, publications by Smith, et al. (1991) and by Roberts, et al. (1991) have demonstrated clear metabolic differences between mouse and rat for the metabolism of butadiene dimer and acrylonitrile respectively. These differences are based on the differences in specific isozymes of cytochrome P-450 which exist between these species. The findings are analogous to the metabolism differences described here and previously for butadiene. I believe the data discussed in this post hearing testimony, as well as the responses to OSHA about the previous data, clearly indicate that the mouse is not predictive of the effects of butadiene in man based on both the metabolism and cytogenetic information currently available.

MGB:jms

November 22, 1991

Table 1

Examples of the Use of Primates as Models in Pharmacological and Toxicological Testing

	Species	Drug
Carcinogenesis	Rhesus, cynomolgus, green and owl monkeys, bushbaby and tree shrew	3-Methylcholanthrene, 2-acetamidofluorene, aflatoxin B, methyl-nitrourea, cyclamate, saccharin, N-nitrosodiethylamine
Treatment of neo-plastic disease	Rhesus and owl monkeys	Prednisolone, vincristine, cytosine arabinoside, cyclophosphamide
Teratogenesis	Rhesus and cynomolgus monkeys Baboon	Thalidomide, testosterone, norethindrone, progesterone, aspirin, meclizine, chlorocyclizine, aminopterin, Thalidomide
Drug dependence	Rhesus monkey Chimpanzee Baboon	Cocaine, amphetamine, opiates, barbiturates Δ^9-Tetrahydrocannabinol Δ^9-Tetrahydrocannabinol
CNS pharmacology	Rhesus monkey Squirrel monkey	Benzodiazepines, meprobamate, chlorpromazine Chlorpromazine, haloperidol
Extrapyramidal toxicity	Rhesus monkey Pig-Tailed monkey	Phenothiazines, reserpine Reserpine
Neurotoxicity	Rhesus monkey	INH, methyl fluoroacetate
Hemotoxicity	Rhesus monkey Baboon	Thiotepa, vincristine, chloramphenicol, nitrogen mustard, 6-mercaptopurine, cycloguanil, cyclophosphamide, S-dichlorovinyl-L-cysteine, methotrexate, chloroethylnitrosurea Chloramphenicol
Immunosuppression	Rhesus monkey	Oxisuran
Gastro-intestinal tract	Rhesus monkey Patas monkey	Thiazides, KCl, calcium gluconate, myalex Myalex
Jaundice	Rhesus monkey Patas monkey	Myalex
Ototoxicity	Pigailed monkey Cynomolgus monkey	Salicylates, kanamycin
Corneal irritation	Rhesus monkey	Anionic, cationic and nonionic detergents
Contraceptive development	Chimpanzee, rhesus, African green, pigtailed and squirrel monkeys, lemur, bushbaby	Estradiol, ethinylestradiol, mestranol, progesterone, megestrol, chlormadinone

From Smith and Caldwell (1977)

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OSHA Docket No. H-041

COMMENTS ON THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH QUANTITATIVE RISK ASSESSMENT FOR 1,3-BUTADIENE

Prepared for

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Washington, DC

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CONTENTS

I. INTRODUCTION

A. Background and Purpose

In 1986, at the request of the Chemical Manufacturers Association (CMA), ENVIRON conducted a detailed assessment of the potential risks to workers from 1,3-butadiene (BD) exposure. The final report of that effort (ENVIRON 1986) is now part of the U.S. Occupational Safety and Health Administration (OSHA) docket for BD. When OSHA announced the public hearings regarding its new proposed rule for BD (OSHA 1990), CMA again approached ENVIRON for assistance with the risk assessment issues raised by occupational BD exposures. ENVIRON prepared a critical review of certain aspects of OSHA's preliminary risk assessment for BD (ENVIRON 1990), commenting specifically on the extent to which certain assumptions and procedures used by OSHA to quantify internal doses and potential human cancer risks in relation to airborne BD concentration were consistent with the substantial body of scientific information regarding BD toxicity and carcinogenicity in laboratory animals and humans. ENVIRON also recommended improved methods for quantifying potential human cancer risks where the approach taken by OSHA appeared deficient in light of current knowledge regarding BD's mechanisms of toxic action.

When the National Institute for Occupational Safety and Health (NIOSH) recently released its own quantitative assessment of these potential risks (Dankovic et al., 1991), CMA requested that ENVIRON critically evaluate similar aspects of the NIOSH report. This document describes ENVIRON's observations and conclusions to date regarding NIOSH's quantitative risk assessment for BD. In reaching our conclusions, we have relied extensively on the detailed technical evaluations of BD toxicology, carcinogenicity, and epidemiology that have been prepared independently by Bird (1990), Bolt (1990), Cagen (1991), and Acquavella (1991).

B. Summary of Principal Conclusions

ENVIRON's principal finding is that there is a strong, scientific basis for concluding that NIOSH's estimates of cancer risk actually overpredict human cancer risks from BD exposure by a substantial margin. This basis is comprised of four distinct elements.

First, the NIOSH assessment assumed that BD uptake would be both complete (i.e., 100%) and identical in rodents and primates. However, data recently published in the peer-reviewed literature indicate that neither BD uptake nor its retention following exposure is complete or the same in rodents and primates when both are exposed to the low concentrations of concern to NIOSH and OSHA. Specifically, data obtained by Bond et al.

(1986) and Dahl et al. (1990, 1991) indicate that BD retention by cynomolgus monkeys immediately following exposure is approximately 10-fold less per unit body weight than is the retention by mice at low airborne BD concentrations. Thus, assuming that BD retention in humans is comparable to that observed in these nonhuman primates, one can also reasonably conclude that humans would experience about 10-fold lower cancer risks than would identically exposed mice. It is important to note that the US EPA has already accepted rodent BD retention data as providing a more relevant measure of exposure than airborne BD concentration for risk assessment purposes (EPA, 1985; Cote and Bayard 1990). A similar conclusion has also been reached by California's Air Resources Board in its recent health assessment of BD (CARB, 1991).

Second, additional data from the same laboratory studies show that cynomolgus monkeys take up (i.e., inhale, absorb, metabolize, and excrete) more than 30-fold less BD per unit body weight than do similarly exposed mice at airborne concentrations of 10 ppm or less. Thus, assuming that the uptake of BD by humans is comparable to that observed in monkeys, one can reasonably conclude that humans would experience about 30-fold lower cancer risks than would identically exposed mice.

Third, the same studies have revealed the existence of significant quantitative differences between species in the metabolism of BD to toxic intermediates. Specifically, BD metabolism occurs much more rapidly in mice than in monkeys. In fact, the mouse exhibits remarkably efficient metabolism of BD to 1,2-epoxybutene-3 even when compared to the rat. Most importantly, Dahl et al. (1990, 1991) demonstrated that blood levels of this highly DNA-reactive and mutagenic intermediate of BD metabolism are over 500-fold lower in monkeys than in mice when both are exposed to low airborne BD concentrations. Thus, using the blood concentration of 1,2-epoxybutene-3 in monkeys as the relevant measure of "delivered" dose, one can reasonably conclude that humans would experience over 500-fold lower cancer risks than would identically exposed mice.

Finally, the findings from epidemiologic studies of BD-exposed workers are fully consistent with the far smaller estimated risks that can be derived by using the measured blood concentrations of 1,2-epoxybutene-3 in monkeys for interspecies extrapolation. While NIOSH has characterized the epidemiologic evidence as being consistent with the findings from the mouse bioassays, direct quantitative comparisons of predicted cancer deaths with observe cancer mortality confirm the near certainty of NIOSH's having significantly overstated the human cancer risks arising from BD exposure.

ENVIRON has therefore concluded that the 1,2-epoxybutene-3 concentrations in the blood of BD-exposed monkeys and rodents provide the best measures of "delivered" dose that are presently available. These data, and the related mechanistic data regarding BD uptake

and retention, indicate clearly that direct use of airborne BD concentrations in risk calculations leads to substantial overstatement of the estimated human cancer risks from BD exposure.

In its risk assessment, NIOSH was highly critical of these data, citing a number of potential methodological and interpretative difficulties with them. NIOSH concluded that these data did not provide valid and relevant measures of BD exposure. Instead, NIOSH employed airborne BD concentrations directly for its risk computations, and, in addition, used the ratio of species body weights raised to the 3/4 power to determine "equivalent" BD doses in humans. This generic scaling factor may be appropriate for interspecies risk extrapolation in certain cases, specifically when chemical-specific data regarding uptake, distribution, and metabolism are unavailable. NIOSH's inappropriate use of this scaling factor served to further increase its estimates of human cancer risk by an approximately 6.5-fold factor.

To achieve a balanced and objective view of the potential human cancer risks posed by BD exposure, NIOSH and OSHA must give full and proper consideration to the mechanistic data regarding interspecies differences in the uptake, retention, and metabolism of BD. In the preamble to its proposed BD standard, OSHA (1990) has stated that such data should be employed for risk assessment purposes:

> "When pharmacokinetic data or metabolic data are available, these data should be used to estimate internal dose. By using all available information, the uncertainty associated with estimating risks across species can be reduced."

Use of these data will clearly yield far lower human cancer risks than NIOSH has estimated. Since the data regarding blood levels of 1,2-epoxybutene-3 provide the best measures of "delivered" dose that are presently available, it is ENVIRON's principal recommendation that NIOSH and OSHA base their estimated human cancer risks on these measurements rather than airborne BD concentration. If instead NIOSH and OSHA continue to base their estimates on calculated amounts of BD absorbed and/or retained, then they must fully and properly account for the differentials in BD uptake and retention that are known to exist between primates and rodents. In either case, a full and proper use of the available mechanistic data regarding BD uptake, retention, and metabolism is certain to yield more accurate estimates of the human cancer risks posed by BD exposure.

II. THE NIOSH APPROACH

NIOSH's "best" estimate of human cancer risk from occupational exposure to BD was derived from a one-stage Weibull time-to-tumor model fit to the prevalence of female B6C3F1 mouse alveolar-bronchiolar neoplasms in certain of the treatment groups from the National Toxicology Program's second BD inhalation bioassay (Melnick et al., 1990). As NIOSH noted, the tumor incidence data from this study must still be regarded as preliminary, since final review of the pathologic evaluations has yet to be completed.

NIOSH chose to employ the female mouse lung tumors for developing their "best" risk estimate because this was the most sensitive site, i.e., because other neoplastic endpoints in male or female mice produced lower estimates of human cancer risk. They also elected to treat these tumors as incidental. In other words, no animal was presumed to have died prematurely from these tumors. Other neoplasms for which NIOSH generated alternative risk estimates included male and female lymphomas and hemangiosarcomas of the heart (both fatal tumor analyses), as well as male and female squamous cell carcinomas of the forestomach, combined Harderian gland adenomas and adenocarcinomas, and combined hepatocellular adenomas and carcinomas (all incidental tumor analyses). In addition, estimates were developed for female mouse mammary gland adenocarcinomas and ovarian granulosa cell neoplasms (both incidental tumor analyses).

NIOSH also elected to disregard the tumor responses in the highest treatment group (625 ppm) from the Melnick et al. (1990) study during the model-fitting process, citing the "strikingly nonlinear" response in this group and the known sublinear metabolism of BD in mice at such high concentrations (Laib et al., 1988). NIOSH did, however, explore the impact of including this high dose group in their analyses. For the female lung tumors, the estimates with the high dose group included are approximately 30% higher than those obtained without it. An alternative analysis in which the female lung tumors were treated as rapidly fatal was also performed, and this again yielded somewhat higher estimates than did the incidental analysis which NIOSH preferred. NIOSH also considered several higher order multistage Weibull models (up to three-stage), but for female lung tumors, these appeared to collapse back to the simpler one-stage form during the model fitting process.

In effecting the extrapolation of risk from mice to humans, NIOSH assumed that both mice and humans would exhibit 100% uptake of the inhaled BD dose. They noted, however, that "Any non-zero value of percent uptake gives an identical final result, provided that uptake is the same in mice and humans." NIOSH also elected to employ a 3/4 power body weight ratio to adjust absolute BD doses (in mg/day) to "equivalency" between the two

species. In other words, NIOSH assumed that humans would experience an approximately 6.5-fold ($(70/.0398)^{1/4}$) greater risk than mice if both species received BD doses throughout life that were identical on a mg/kg/day basis.

III. IMPLICATIONS OF MECHANISTIC DATA FOR HUMAN CANCER RISK

A. Data Regarding Retention of BD

In a recent report, Dahl et al. (1990) published findings that are highly relevant to the amounts of BD that are retained by rodents and primates following inhalation exposure. B6C3F1 mice and Sprague-Dawley rats had been previously exposed identically to 7 ppm BD for 6 hours (Bond et al., 1986). Male monkeys (Macaca fascicularis) were therefore exposed for 2 hours to 10 ppm BD for interspecies comparison purposes. When Dahl et al. normalized the amount of retained BD to the different species body masses and expressed retained BD on a per 10 ppm-hour basis, the measured BD retention rates were determined to be 5.27, 0.46, and 0.52 μmol/kg/hr/10 ppm in the mouse, rat, and monkey respectively. It should be noted here that the mouse retention value was incorrectly reported to be 3.3 μmol/kg/hr/10 ppm as a consequence of an typographical error in a previous paper (Bond et al., 1986) (personal communication from Dr. Alan Dahl).

It is clear from these observations that these species would not absorb and retain the same BD dose per unit body mass if they were identically exposed to the same airborne BD concentration. Rather, the mouse would retain a BD dose that is approximately 11-fold higher (5.3/0.46) than that retained by the rat, and 10-fold higher (5.3/0.52) than that received by the monkey. It is therefore reasonable to conclude on the basis of BD retention differences that rats and monkeys would be at significantly less risk of developing cancer than mice if all were identically exposed to the same airborne BD concentration because they would absorb and retain significantly less BD per kilogram of body mass than do mice.

Because the human species is much more closely related, both anatomically and physiologically, to the monkey than the mouse, it is entirely reasonable to expect that humans would also retain significantly less BD than would identically exposed mice. Indeed, were this the only relevant information available regarding BD disposition in different species, it would argue that the rat provides a better animal model than the mouse for evaluating human cancer risk from BD exposure.

The presence of the endogenous MuLV retrovirus in the B6C3F1 mouse and its activation by BD exposure raises additional questions with regard to the relevance to human cancer risk of any carcinogenic response in this mouse strain. While it is known that the retrovirus plays a significant modulating role in the incidence of thymic lymphoma (Irons, 1987), it is also possible that activation of the retrovirus by BD influences the incidence of other tumor types as well. Consequently, even though NIOSH has based its "best" estimates of risk on the incidence of lung neoplasms among female mice, there is still great uncertainty

regarding the relevance of these estimates to the potential human cancer risks from BD exposure, especially in quantitative terms. ENVIRON therefore continues to believe that scientifically defensible risk estimates can and should be derived from the Hazleton Laboratories rat study (HLE, 1981). Indeed, such estimates are likely to be less uncertain than any that could be obtained from either of the NTP mouse bioassays, even with appropriate corrections for the known high to low dose and interspecies differences in BD pharmacokinetics.

It is important to note here that in contrast to the NIOSH assessment, OSHA has relied on mouse BD retention data in generating its "best" estimates of risk (OSHA, 1990). EPA has also accepted the BD retention data reported by Bond et al. (1986) as providing a more relevant measure of exposure for risk assessment purposes than airborne BD concentration (EPA, 1985; Cote and Bayard 1990). A similar conclusion has also been reached recently by California's Air Resources Board in its health assessment of BD (CARB, 1991). NIOSH should therefore also adjust its human cancer risk estimates downward by an approximately 10-fold factor at a minimum so as to properly account for the smaller retention of BD by primates relative to the mouse. Clearly, it is altogether appropriate for NIOSH to make full and proper use of this important information in developing its "best" estimates of risk based on either the mouse or rat data.

B. Data Regarding BD Uptake

Very recently, additional highly relevant information regarding the uptake of BD by rodents and primates has been published in the peer-reviewed literature. Specifically, Dahl et al. (1991) exposed male cynomolgus monkeys (Macaca fascicularis) for 2 hours to 10, 310, and 7760 ppm of ^{14}C-labeled BD and estimated BD uptake as a percentage of the amount of BD inhaled. Uptake was determined by combining all radiolabeled materials excreted in urine and feces as well as via exhalation (other than BD itself) (only the residual ^{14}C that still remained in the monkey's bodies at the end of the 96 hour postexposure collection period was not included). Thus, the new Dahl et al. (1991) uptake data provide additional comprehensive measures of inhaled and absorbed BD doses. At approximately 10 ppm, monkey uptake was determined to be only 2.9% of inhaled BD, or 0.13 nmol/min kg^{-1} ppm^{-1}.

For comparison purposes, Dahl et al. also estimated BD uptake in Sprague-Dawley rats and B6C3F1 mice by graphical interpolation between the data points presented in Figure 4 of the earlier report by Laib et al. (1988). Dahl et al.'s BD uptake estimates for approximately 10 ppm exposures were 2.8 nmol/min kg^{-1} ppm^{-1}, or 15%, for rats, and 5.2

nmol/min kg^{-1} ppm^{-1}, or 12% for mice.

BD uptake in rodents may also be estimated directly from Table 1 of the Laib et al. (1988) report, which provides estimates of BD metabolized by rats and mice under the conditions of the two earlier bioassays (HLE, 1981 and NTP, 1984). It is important to note that because uptake is saturable, these estimates for high dose conditions are likely to understate rodent uptake at the lower BD doses of concern to NIOSH and OSHA. Using Laib et al.'s estimate of 140 μmol/kg per hour for rats exposed to 1000 ppm, we obtain an estimated uptake rate of 2.3 nmol/min kg^{-1} ppm^{-1}, or 12.7% of the BD inhaled. Using Laib et al.'s corresponding estimate of 165 μmol/kg per hour for mice exposed to 625 ppm, uptake is 4.4 nmol/min kg^{-1} ppm^{-1}, or 9.3% of the BD inhaled.

These estimates demonstrate clearly that BD uptake is nowhere near 100% in rats, mice, or monkeys, in contrast to the assumption made by NIOSH. The rat has the highest uptake of these three species, but that rate is nevertheless still only about 13% of the BD inhaled. Furthermore, if one compares these percentages across species, there is a significant difference between the rodents and the primate, with the monkey (2.9%) exhibiting 3-fold less uptake than the mouse (9.3%) and 4-fold less than the rat (12.7%).

The contrast between uptake in monkeys and mice is even more dramatic when it is expressed per unit body weight: BD uptake in the monkey (0.13 nmol/min kg^{-1} ppm^{-1}) is more than 30-fold smaller than that in the mouse (4.4 nmol/min kg^{-1} ppm^{-1}). Thus, assuming that BD uptake in humans is comparable to the BD uptake observed in monkeys, one can reasonably conclude that humans would experience more than 30-fold (4.4/0.13) lower cancer risks than mice when both are exposed identically to BD. Even allowing, as NIOSH did, for the difference between bioassay and occupational exposure regimens, simple correction for the differential in BD uptake percentages between mice and monkeys would lead to more than 14-fold lower estimated risks than NIOSH has projected with the generic 3/4 power body weight scaling rule for extrapolating estimated cancer risk between species.

C. Data Regarding DNA-Reactive BD Metabolites

The metabolism and pharmacokinetics of BD have been described in considerable detail by other commenters (see particularly the testimony before OSHA and additional posthearing comments of Dr. Michael Bird as well as ENVIRON's earlier BD reports (ENVIRON 1986, 1990)). Here we only summarize certain critical facts that appear to be highly relevant to the quantitation of estimated human cancer risk from BD exposure.

The first step in BD metabolism, oxidation of BD to the monoepoxide 1,2-epoxybutene-3, was first demonstrated with hepatic microsomes over ten years ago by

Malvoisin et al. (1979). Subsequently, these investigators demonstrated further oxidation in vitro of 1-2-epoxybutene-3 to 1,2:3,4-diepoxybutane, as well as the epoxide hydrolase-mediated reduction of 1,2-epoxybutene-3 to 3-butene-1,2-diol, followed by second oxidation step yielding 3,4-epoxy-1,2-butane-diol. The 1,2-epoxybutene-3 intermediate is a monofunctional alkylating agent, while 1,2:3,4-diepoxybutane is bifunctional and is known to form DNA-DNA crosslinks. Both of these metabolites of BD are DNA-reactive intermediates that also show mutagenic activity in bacterial and other test systems, while BD per se does not. Thus, both may play critical roles in the carcinogenicity of BD. It is therefore especially important to establish accurately the quantitative relationships between airborne BD concentrations and corresponding internal "delivered" doses of these BD metabolites for the relevant species.

An extensive series of studies by Bolt and colleagues (c.f., Laib et al. 1990) has confirmed the production of 1,2-epoxybutene-3 following in vivo BD exposure, and further established the saturable character, at least at high airborne BD concentrations ($>$ 1000 ppm) of the initial conversion of BD to this monoepoxide in both rats and mice. These investigators also determined that at lower airborne BD concentrations, where linear pharmacokinetics prevail, mice metabolize BD to 1,2-epoxybutene-3 at about twice the rate as do rats. In addition, they determined that the subsequent metabolism of 1,2-epoxybutene-3 is saturable in mice at a far smaller rate (350 μmol/kg/hr) than in rats ($>$ 2600 μmol/kg/hr). Taken together, these findings imply that internal concentrations of 1,2-epoxybutene-3 should reach much higher levels in mice than in rats when both are identically exposed to airborne BD. In fact, Laib et al. (1990) have concluded that the limited 1,2-epoxybutene-3 detoxication capacity of mice relative to that of rats is a critical determinant of the higher susceptibility of mice to BD-induced carcinogenesis. Knowledge of internal concentrations of 1,2-epoxybutene-3 is thus essential to the development of accurate estimates of the cancer risks posed by BD exposure.

The study of Bond et al. (1986) and the more recent studies by Sun et al. (1989) and Dahl et al. (1990 and 1991) have both developed significant new information regarding quantitative differences among species in the internal concentrations of several BD metabolites. The Sun et al. (1989) and Dahl et al. (1990 and 1991) studies are of particular interest, since they report comparative measurements of blood levels of the mutagenic 1,2-epoxybutene-3 obtained not only in mice and rats, but also in monkeys, following inhalation exposures to BD for 2 hours.

Specifically, B6C3F1 mice had been previously exposed to 7 and 70 ppm BD, while Sprague-Dawley rats had been exposed to 70 ppm BD (Bond et al., 1986). In addition, cynomolgus monkeys were exposed to 10 ppm BD (Sun et al., 1989; Dahl et al., 1990 and

1991). These investigators determined that monoepoxide levels in the blood of mice and rats identically exposed to 70 ppm BD were 28.6 ± 0.7 and 5.7 ± 0.6 pmol/ml/ppm respectively (blood epoxide levels were normalized by airborne BD concentrations, i.e., expressed per ppm BD, so as to permit direct comparisons even when the different species were not identically exposed). Thus, at 70 ppm BD, mice exhibited approximately 5-fold higher 1,2-epoxybutene-3 levels in their blood than did rats. Even more importantly, in the concentration range of interest to NIOSH and OSHA, mice exposed to 7 ppm BD exhibited 85.7 ± 14.3 pmol/ml/ppm of 1,2-epoxybutene-3 in their blood, while monkeys exposed to 10 ppm exhibited only 0.16 ± 0.05 pmol/ml/ppm (Sun et al. (1989) Table 1). It must be noted here that the monkey blood level was inadvertently reported as 0.13 pmol/ml/ppm in Dahl et al. (1990). This error was corrected in the Dahl et al. (1991) report.

The findings from these studies indicate that mice developed approximately 536 ± 190-fold higher blood concentrations of 1,2-epoxybutene-3 than did similarly exposed monkeys. Thus, making the reasonable assumption that humans metabolize BD in the same manner as monkeys, the Sun et al. (1989) and Dahl et al. (1991 and 1991) results imply that humans should be approximately 536-fold less sensitive to BD's carcinogenicity than are mice.

A similar conclusion can be drawn from a comparison of the rat and monkey blood epoxide levels observed by Sun et al. (1989) and Dahl et al. (1990 and 1991). Specifically, rats exposed to 70 ppm exhibited 5.7 ± 0.6 pmol/ml/ppm blood epoxide, while monkeys similarly exposed to 10 ppm exhibited only 0.16 ± 0.05 pmol/ml/ppm blood epoxide, as noted above. Again, provided that humans metabolize BD in the same manner as monkeys (as has been indicated by the limited data reported by Schmidt and Loeser (1986)), these data show that humans should be more than 35 ± 11.7-fold less sensitive to BD's carcinogenicity than are rats.

When EPA conducted its risk assessment for BD (EPA, 1985), the best data available regarding internal doses of BD or its metabolites were the preliminary estimates of retained BD percentages obtained from a Lovelace Institute report (NTP 1985) that had not yet been published in the peer-reviewed literature. As was noted previously however, OSHA also utilized this preliminary information in constructing its estimates of human cancer risk. The new data of Sun et al. (1989) and Dahl et al. (1990 and 1991) regarding internal 1,2-epoxybutene-3 concentrations now provide a much superior alternative measure of "delivered" dose even relative to the updated BD retention data. This highly reactive and mutagenic epoxide metabolite is far more likely to be responsible for the carcinogenicity of BD than is BD per se. It is therefore strongly recommended that NIOSH and OSHA both utilize these new pharmacokinetic data in extrapolating their risk estimates from mice and rats to humans.

A summary of the approximate impacts on risk estimates of using the different measures of "delivered" BD doses discussed in this and preceding sections is provided in Table 1.

TABLE 1

Approximate Impact of Different Measures of "Delivered" Dose on NIOSH's Best Estimate of Cancer Deaths Per 10,000 Workers Exposed for a Working Lifetime to 2 ppm BD

NIOSH Current "Best" Estimate	597.
Adjusted for Retention	58.9
Adjusted for Uptake	11.6
Adjusted for BD Metabolism to 1,2-epoxybutene-3	1.1

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D. 3/4 Power Body Weight Scaling Between Species

As was noted previously, ENVIRON's principal conclusion is that the extensive pharmacokinetic data regarding species differences in BD uptake, distribution, and metabolism provide valid, useful, and highly relevant measures of BD exposure for risk assessment purposes. Nevertheless, NIOSH rejected use of these data and elected instead to employ airborne BD concentrations directly for its risk computations, calculating BD uptake assuming 100% absorption irrespective of the species being considered. In addition, NIOSH used the ratio of species body weights raised to the 3/4 power to extrapolate from rodent BD doses to "equivalent" BD doses in humans.

This particular allometric scaling rule has been suggested as plausible on empirical (Travis and White, 1988) and theoretical (O'Flaherty, 1989 and Travis et al., 1990) grounds (the latter specifically for direct acting carcinogens that do not require metabolic activation, as does BD), but only when specific pharmacokinetic data regarding chemical distribution and disposition are not available.

In fact, the available comparative data regarding BD uptake and metabolism across species directly contradict the predictions of this empirical scaling rule. Because rats and monkeys are much larger than mice, the 3/4 power body weight scaling rule predicts that these species should be more sensitive to BD than mice. Yet, as NIOSH has itself noted, exactly the opposite is the case: rats and monkeys are both markedly less sensitive to BD than mice, first because mice are remarkably efficient in metabolizing BD to 1,2-epoxybutene-3, and second, because they are remarkably inefficient at detoxifying this highly DNA-reactive intermediate of BD metabolism. This issue is discussed in considerably greater detail in the comments of Bird (1991), Bolt (1990), and Cagen (1991). The clear implication of the well-established interspecies differences in BD uptake and metabolism is that the 3/4 power body weight scaling rule is altogether inappropriate for use in interspecies extrapolation of estimated BD cancer risks.

IV. COMPARISON OF PREDICTED AND OBSERVED HUMAN RISKS

In its 1990 assessment, OSHA expressed concern that by relying upon the female mouse heart hemangiosarcoma data for its "best" estimate of risk, it might be underestimating BD's carcinogenic potential. Indeed, it called attention to the fact that its "best" risk estimate of 128/10,000 at 10 ppm BD was lower than almost all of the other estimates that had previously been derived from the first NTP mouse bioassay. Now NIOSH has produced "best" estimates of human cancer risk that are significantly higher than OSHA's, and it has called attention to the "consistency" of the increased incidence of lymphopoietic neoplasms seen in certain epidemiologic studies of exposed worker populations with the high lymphoma incidence observed in the two mouse bioassays. NIOSH did not however undertake a quantitative comparison of its risk estimates with existing human cancer mortality data. Such a comparison can prove useful in objectively assessing the plausibility of NIOSH's "best" estimates of human cancer risk from BD exposure.

EPA (1985) described a consistency check for its "point" estimate of lifetime cancer risk using the Meinhardt et al. (1982) and Matanoski et al. (1982) studies of worker mortality in the styrene-butadiene rubber (SBR) industry. Results from similar quantitative comparisons have also been reported previously by ENVIRON (1986 and 1990) and Acquavella (1990). For example, Table 2 presents the probabilities of observing as few or fewer deaths from any cancer, respiratory tract cancer, or lymphopoietic cancer as were actually observed among the 3,124 SBR production workers as reported by Matanoski et al. (1990), assuming that the true cancer risks arising from this group's BD exposures were equal to the NIOSH "best" estimates for 10, 5, 2, or 1 ppm BD, but with exposure only for 10 of 50 working years and with followup only for 21 of the 50 remaining years of life. As has been discussed previously (ENVIRON, 1986 and 1990; Acquavella, 1990), BD exposure levels in the SBR industry probably averaged 10 ppm or higher for these workers, so the predicted numbers of deaths appearing in Table 2 will most likely understate the extent of any inconsistencies between the observed number of cancer deaths and NIOSH's predictions.

Nevertheless, it is clear that NIOSH's "best" risk estimates are altogether inconsistent statistically with the observed numbers of deaths in this SBR worker group from any cancer, respiratory tract cancer, or lymphopoietic cancer, even with exposure levels as low a 1 ppm. Similar conclusions were reached by Acquavella (1991) in his objective comparison of NIOSH "best" estimates of risk with the observed cancer mortality in the World War II Texaco subcohort described by Divine (1990).

It is important to note in this regard that the significant inconsistencies between observed and NIOSH-predicted cancer deaths are readily apparent despite Matanoski et al.'s acknowledged understatement of the expected number of deaths in the absence of BD exposure (Matanoski et al., 1990), and despite not having considered the maintenance workers from their study in this comparison. Had the subgroups of production and maintenance workers been combined appropriately, the inconsistencies between observed and NIOSH-predicted cancer deaths in this larger group would have been even more extreme than those presented in Table 2.

The epidemiologic observations thus indicate that NIOSH has significantly overstated the human cancer risks arising from BD exposure. In fact, the NIOSH "best" estimates are altogether inconsistent with the actual observations in the Matanoski et al. (1990) production workers even assuming that BD exposures averaged about 1 ppm. While the epidemiologic data are not sufficiently powerful to categorically reject predicted risks as small or smaller than OSHA's previous "best" estimate, they are also entirely consistent with the far smaller risks that are predicted by full and proper utilization of the BD absorption, retention, and metabolism differences that are now known to exist between rodents and primates.

TABLE 2

Consistency Check of NIOSH BD Cancer Risk Estimates
Based on Observed Cancer Deaths Among
3,124 Production Workers
(Matanoski et al., 1990)

	All Cancers	Respiratory Tract Cancers	Lymphopoietic Cancers
Observed Deaths	124	49	19
Expected Deaths with 10 ppm	205.3	116.5	82.5
p-value	2.5×10^{-10}	7.4×10^{-13}	3.2×10^{-17}
Expected Deaths with 5 ppm	172.7	83.9	49.9
p-value	1.8×10^{-5}	1.1×10^{-5}	3.2×10^{-7}
Expected Deaths with 2 ppm	151.4	62.6	28.6
p-value	0.0025	0.012	0.015
Expected Deaths with 1 ppm	143.9	55.1	21.1
p-value	0.0084	0.040	0.082

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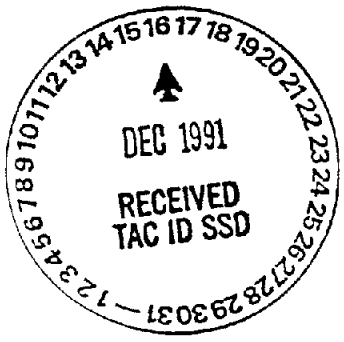

Genevieve Shiroma, Chief
Toxic Air Contaminant
Identification Branch
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Ms. Shiroma:

Attached, please find General Motors comments on the California Air Resources Board revised draft report titled Proposed Identification of 1,3-Butadiene as a Toxic Air Contaminant, dated October 1991. General Motors comments focus on the following three points:

- The report does not properly inform the reader that the risk from motor vehicle 1,3-butadiene emissions has been reduced dramatically over the past 20 years and will continue to decrease substantially over the next 20 years from fuel and vehicle regulations already on the books.

- The report does not provide the proper perspective on the risk from motor vehicles relative to the much larger risks from indoor sources, particularly that of both smokers and nonsmoker from cigarette smoke and environmental tobacco smoke; and

- The report should better portray the limitations and uncertainty associated with the range of unit risk factors developed for 1,3-butadiene.

If you have any questions concerning these comments, please contact J. M. Heuss of my staff at 313-947-2787.

Sincerely,

Samuel A. Leonard, Director
Automotive Emission Control

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GENERAL MOTORS COMMENTS ON PROPOSED IDENTIFICATION OF 1,3-BUTADIENE AS A TOXIC AIR CONTAMINANT BY THE STATE OF CALIFORNIA SRP VERSION DRAFT, OCTOBER 1991

General Motors (GM) has reviewed the October 1991 draft prepared by the Staffs of the Air Resources Board and the Office of Environmental Health Hazard Assessment and offers the following comments. While some of the recommendations provided by GM on the preliminary draft (SM-2059, letter from S. A. Leonard to Genevieve Shiroma, March 22, 1991) have been incorporated in the new draft, GM is still concerned that the risk from present and future 1,3-butadiene concentrations is not put into the proper perspective. First, the limitations and uncertainty associated with the range of unit risk factors developed for 1,3-butadiene should be better portrayed to the reader, especially in the Executive Summary. Second, additional detail should be added to inform the reader that the risk from motor vehicle 1,3-butadiene emissions has been reduced dramatically over the past 20 years and will be reduced substantially over the next 20 years from fuel and vehicle regulations already on the books. Third, additional perspective should be added on indoor exposures, in particular to the substantial exposures of both smokers and nonsmokers to direct cigarette smoke and environmental tobacco smoke (ETS).

Comments on Executive Summary

Risk Assessment. GM is concerned that the uncertainties and limitations of the risk calculations in Part B are not put in the correct perspective for the reader. The Part B Summary refers to "theoretical human risks associated with a continuous lifetime exposure to butadiene in ambient air." Unit risks based on rat and mouse inhalation studies varied by two orders of magnitude. Therefore, Part B indicates that "community exposure to ambient butadiene at currently detected levels could be associated with an upper limit of 4 to 666 additional lifetime cancers per million exposed individuals. While some of these important caveats to the risk calculation are put in the Executive Summary, there is still a statement that "An estimated 3,936 1,3-butadiene-induced cancers statewide are expected to occur at average ambient concentrations." Because statements like this can be taken out of context, the words "upper limit" should be included in each reference to the risk.

GM is concerned that there is such a wide range (nearly two orders of magnitude) in the upper limit risk based on different animal

models. The large uncertainty in the upper limit risk means that there is the same large uncertainty in judging the need for and cost-effectiveness of any additional measures to reduce the risk. It is, therefore, extremely important to establish which animal model more closely approximates the risk to humans. A better understanding of the mechanism or mechanisms of 1,3-butadiene carcinogenicity is thus of paramount importance. The reader of the Executive Summary should be clearly informed of the wide range in the upper limit risk, and the reasons for it.

GM is concerned that the upper limit risk calculations in Part B do not provide an assessment of the actual risks that Californians experience as they are exposed to 1,3-butadiene in their daily lives. A knowledge of the relative contributions of individual sources is important for better estimates of public exposure. In the 1980's, the U.S. EPA introduced a new conceptual model of total human exposure (TEAM) and used it to compare benzene emissions vs. exposures. The analysis indicated that although motor vehicles emitted 82 percent of benzene emissions, they were responsible for only 18 percent of individual exposures based on personal monitoring.[1] The TEAM study showed how significant individual sources of exposure are because the general public spends most of its time indoors.

GM reiterates its recommendation that as ARB evaluates the risk from exposure to 1,3-butadiene and other airborne toxics, it consider the findings and recommendations from several important reports and reviews by eminent scientific groups. In particular, EPA's Science Advisory Board (SAB) has recently recommended that the Agency should target its environmental protection efforts on the basis of opportunities for the greatest risk reduction.[2] In order to set priorities, the SAB indicated that the Agency "must weigh the relative risks posed by different environmental problems, determine if there are cost-effective opportunities for reducing those risks, and then identify the most cost-effective risk reduction options." Further, the SAB recommended that EPA improve the data and analytical methodologies that support risk assessment and comparison, indicating that risk rankings should be based on total human exposure to specific toxic agents.

A recent National Research Council (NRC) review of human exposure assessment for airborne pollutants came to similar conclusions.[3] The NRC committee wrote that "risk reduction strategies that address only outdoor air are only partially effective. Such strategies need to be modified to better address the importance of indoor exposures." To set priorities for reducing risk to potentially harmful pollutants, the committee indicated that all

media and all routes of exposure must be assessed.

In response to such recommendations, a high-level interagency working group has been formed at the federal level to coordinate risk assessment practices across different federal agencies, under the auspices of the Office of Science and Technology Policy (OSTP) Federal Coordinating Council on Science, Engineering and Technology. The goal is to improve, harmonize, and minimize the uncertainties in risk assessment. Among the activities is a review of the 1985 OSTP Document on Carcinogenicity.

Under Section 206 of the Clean Air Act, the U.S. Environmental Protection Agency is carrying out a study of the need for controlling emissions of mobile-source related toxics including 1,3-butadiene. A workshop to outline the research needs for 1,3-butadiene and other mobile-source toxics will be part of that effort. GM urges the ARB to participate in and coordinate its efforts with these federal efforts to improve, harmonize, and reduce the uncertainty in risk assessment.

As ARB enters the risk management phase of its consideration of 1,3-butadiene and other airborne toxics, GM recommends that decisions be made based on improved methodologies for risk assessment that account for the real exposures that Californians experience as they move about in their daily life rather than on theoretical upper limits for exposure scenarios that are not realistic.

Emission Trends. The question "Are emissions of 1,3-butadiene expected to increase in the state?" should be restated as "What are past, current, and expected future emissions of 1,3-butadiene?" The answer to the question should document the significant emission reductions that have occurred over the past 20 years and are expected over the next 20 years. On page 573 of Part C, in response to the earlier GM comments on this issue, the statement is made that "Staff agree that hydrocarbon concentrations have been dramatically reduced in the Los Angeles Basin since the 1960's as the direct result of increased motor vehicle emissions control and reductions in emissions from industrial sources." This statement should be part of the Executive Summary, not relegated to page 573 of Part C.

Evidence that current ambient concentrations are only a fraction of the ambient concentrations that existed 20 years ago should be included in Part A. Altshuller, et al.[4] measured individual hydrocarbons in several hundred samples collected in Los Angeles over several months in the fall of 1967 and reported 1,3-butadiene

concentrations averaging 2 ppbv with 10 percent of the values exceeding 5 ppbv. Similarly, the average 1,3-butadiene concentration in 218 samples analyzed by the Los Angeles Air Pollution Control District in 1965 was 2 ppbv.[5] Thus, the current 1,3-butadiene concentrations in Los Angeles are roughly one-quarter of the concentrations measured in the middle-to-late 1960's. This dramatic reduction in ambient concentrations occurred in spite of increasing population, numbers of vehicles or vehicle miles travelled and is a clear indication of the success of the emission controls on motor vehicles.

As noted in the comments on Part A, the continuing reductions in emissions anticipated with current regulations should be quantified and summarized in the Executive Summary. In particular, the 26 to 29 percent reduction in emissions from gasoline-powered motor vehicles anticipated when Phase 2 gasoline is introduced should be highlighted. The combination of dramatic reductions to date and continuing reductions over the next 20 years provides important information for the reader that puts the risks from ambient exposures in a temporal perspective.

Indoor Exposures. In response to the question "What about indoor exposure to 1,3-butadiene?," the Executive Summary indicates that indoor air may be the major route of exposure to 1,3-butadiene for those individuals exposed to a heavy smoking environment. Based on the available data it is clear that indoor air <u>is</u> the major route of exposure to 1,3-butadiene for smokers as well as those exposed to a heavy smoking environment and that exposure to environmental tobacco smoke (ETS) <u>is</u> a major route of exposure to 1,3-butadiene for Californians. An estimate of the average daily intake of 1,3-butadiene from ETS is made in the comments to follow; it is 2.8 times the daily intake from the population-weighted statewide average ambient 1,3-butadiene concentration. GM recommends that the answer to this question include comparisons of the average daily intake of 1,3-butadiene from smoking, typical exposures to ETS, heavy exposure to ETS, and exposure to ambient air.

The statement that non-smoking residential exposures may typically be close to the statewide average ambient exposure is not supported by the data provided. The analytical technique used in the Woodland study did not have sufficient sensitivity to discriminate between residential exposures above, at, or below the statewide ambient average concentration. Therefore, the statement should be removed and replaced with one that acknowledges that there is not enough information to make a quantitative comparison between ambient exposures and non-smoking residential exposures.

Comments on Part A Exposure Assessment

Emissions. In previous comments (SM-2059), GM recommended that data from the Auto/Oil Air Quality Improvement Program (AQIRP) be used to provide a better basis for statistically robust mobile source inventories. Instead, ARB staff used unpublished data[6] to estimate that 1,3-butadiene emissions from catalyst-equipped vehicles are 0.59 weight percent of Total Organic Gas (TOG) emissions. GM continues to believe that it is important to include the AQIRP data, especially because a portion of the data was obtained from vehicles operating on the "industry average gasoline" that ARB has accepted for use in calculating reactivity adjustment factors. The extensive AQIRP data on industry average gasoline for both current and older vehicle fleets demonstrate that 1,3-butadiene is a smaller percentage of TOG than the unpublished ARB data indicate. For example, the average wt. percent of 1,3-butadiene for current (1989) catalyst-equipped vehicles is 0.38 percent of TOG and for older (1983-1985) catalyst-equipped vehicles it is 0.34 percent.[7] The massive additional data on reformulated gasolines also suggests that 1,3-butadiene is between 0.3 and 0.4 wt. percent of TOG rather than 0.59, adding substantial credence to use of the AQIRP database. Inclusion of the AQIRP data would lower the estimate of emissions from catalyst-equipped vehicles substantially.

GM made a recommendation in its March 1991 comments that can help test the accuracy of the mobile source inventory. GM pointed out that:

> "There is another way that the SCAQS data can be used -- to verify overall estimates of 1,3-butadiene emissions from vehicular sources. The SCAQS data can be used to estimate the fraction of 1,3-butadiene in ambient non-methane organic carbon concentrations. In a similar data base involving several hundred samples collected in 1987 in 32 cities, Lonneman found that 1,3-butadiene represented 0.22 wt percent of the carbon in the samples.[8] The analogous fraction of carbon in the SCAQS samples can be used to check the estimated statewide emissions of 1,3-butadiene."

GM recommends that early morning SCAQS 1,3-butadiene/TOG ratios be analyzed to shed light on the ARB's estimated inventory.

The staff response (on page 567 of Part C) to GM's earlier recommendation to use the AQIRP data neglects to mention the industry average gasoline data and indicates that the gasolines used in AQIRP are prototype. However, the ARB's recent Phase 2

gasoline regulatory package used the AQIRP data to estimate that a 26 to 29 percent reduction in 1,3-butadiene emissions will be associated with Phase 2 gasoline.[9] Thus Phase 2 gasoline, because it will be introduced throughout the state and used throughout the vehicle fleet, will substantially reduce statewide 1,3-butadiene emissions.

The anticipated success of phase 2 gasoline in reducing the emissions of and risk from 1,3-butadiene raises the possibility that additional changes to gasoline may provide cost-effective reductions in 1,3-butadiene emissions. As Part A correctly points out, 1,3-butadiene is not a significant component of gasoline, rather it is formed during the combustion of other components. Based on the known mechanism of hydrocarbon oxidation at temperatures representative of the blowdown and exhaust processes in an engine,[10] 1,3-butadiene should be produced principally by hydrogen atom abstraction from a saturated carbon atom on a straight-chain alkene. Dryer and Brezinsky[11] provide evidence for such a mechanism in experiments that show that 1,3-butadiene is a significant intermediate oxidation product on n-octane but not of its isomer 2,2,4-trimethlypentane. Another route to butadiene could involve decomposition of a butene. 1,3-butadiene can also be formed from the partial oxidation of aromatic hydrocarbons. Venkat, et al.[12] have shown that butadiene is present as an intermediate in the oxidation of benzene, toluene, and ethylbenzene.

GM recommends that information on the formation of 1,3-butadiene be included in Part A, both in terms of the chemical mechanisms involved and the experimental findings from the AQIRP that have identified the effects of changing variables such as olefins, aromatics, T90, etc. An understanding of the mechanisms of 1,3-butadiene formation may lead to further composition changes that can materially reduce 1,3-butadiene.

There is an additional small source of 1,3-butadiene emissions that should be included in the inventory. The draft report alludes to the possibility that 1,3-butadiene may be released to the environment as tires wear, but indicates that there is not enough information to support or deny the theory. In contrast, Cadle and Williams[13] positively identified 1,3-butadiene and five other monomers and dimers of styrene-butadiene rubber copolymers as gaseous emissions from tire wear. Although the emission rate of 1,3-butadiene was below 0.1 mg/km/tire in average wear conditions, this small emission should not be neglected. The results presented by Cadle and Williams lump 1,3-butadiene and isoprene emissions together, but 1,3-butadiene was positively identified in additional

chromatographic separations.

Emission Projections. The text correctly indicates that 1,3-butadiene emissions are expected to steadily decrease through 2010 with the current regulations. However, it would be useful to provide a quantitative estimate of the decrease to put the risk from current and expected future exposures in perspective. The recent Phase 2 gasoline regulatory package included estimates of future trends in emissions of Volatile Organic Compounds, showing a reduction from 1400 tons per day in 1987 to 260 tons per day in 2010 for on-road gasoline-powered motor vehicles.[14] With such substantial reductions anticipated from existing regulations, the accompanying 1,3-butadiene reductions should also be substantial.

Ambient Exposures. GM continues to believe that the individual organic species data from SCAQS should be analyzed in terms of spatial and temporal variability to provide input for more refined exposure analyses. The staff comments (Part C, page 572) indicate that the risk management phase of the 1,3-butadiene project will consider all sources for their impact on the population. In order to properly account for the population exposure to 1,3-butadiene, spatial and temporal differences in ambient concentrations as well as indoor concentrations will need to be taken into account.

Along the same lines, GM is concerned that ambient exposures from urban monitoring is used to characterize the total population of California. A portion of the population resides in more rural locations where the 1,3-butadiene concentrations are expected to be below typical urban levels. If this is taken into account, the statewide average ambient exposure and accompanying risk would be reduced somewhat.

Indoor Concentrations. GM is encouraged that the current draft includes additional information on exposures to 1,3-butadiene from indoor sources such as environmental tobacco smoke. However, the statement that "it appears reasonable to assume that residential exposures ... may typically be close to ambient levels" is not supported by the data provided. Because the detection limit used in the Woodland study (0.54 ppb) is significantly above the statewide average ambient exposure, no statement about whether residential exposures are above or below ambient can be made. GM strongly encourages ARB to carry out a study of residences, offices, and commercial spaces using a technique that has a detection limit similar to that of the Woodland pilot study (0.05 ppb). Such measurements, in conjunction with estimates of smoking, would go a long way toward establishing the exposures that

Californians experience during the 80 percent or so of the time they are indoors as well as the sources of those exposures.

The draft indicates that there is not sufficient information to make a quantitative analysis of total human exposures at this time. Nevertheless, the draft includes reference to several data sources that can be used to provide some perspective on the exposures from ETS. Obviously, for the 30 percent of persons over 18 that are current smokers, the exposure to 1,3-butadiene from smoking overwhelms that from any other sources. For the roughly equal portion of the population that are former smokers, their lifetime exposure to 1,3-butadiene has probably also been dominated by their smoking experience. For non-smokers, the exposure to ETS is not insignificant. Survey information referenced in the preliminary draft report indicated that Californians are exposed to ETS approximately 2.6 hours each day on the average. Because this is (probably) self-reported exposure, it represents exposure over some threshold. In addition, the draft indicates that about four percent of California residents reported attending bars and nightclubs. Lofroth, et al.[15] have estimated that the inhaled dose in two hours in such conditions is in the range of 18 to 32 ug/exposure. For comparison, the daily inhaled dose from the statewide ambient concentration reported in the draft is 16.4 ug. Lofroth, et al. also report measurements of the airborne yield of 1,3-butadiene from sidestream smoke of 400 ug/cigarette. When one considers that roughly 70 billion cigarettes are smoked in California each year -- for the most part indoors -- the potential for significant exposure of non-smokers to 1,3-butadiene from ETS is apparent.

While GM agrees that there is not sufficient information to make a complete, quantitative analysis of the risk from outdoor vs. indoor sources at this time, GM submits that there <u>is</u> sufficient information to estimate total daily intake of 1,3-butadiene from ETS -- or passive smoking as it is also called -- when the information in Lofroth, et al. is combined with the extensive body of existing information on the exposure to ETS. Estimates of the typical daily intake of various toxic constituents of cigarette smoke for both active and passive exposure were provided as an attachment to SM-2059 (Part C, page 357, Table C-3 from Appendix C of EPA's May 1990 review of the health effects of passive smoking).[16] While it is recognized that exposure to ETS varies widely due to differences in the rate of smoking, types of cigarettes smoked, room volumes, and ventilation rates in indoor environments, the EPA calculated a "typical" exposure condition using representative values of the composition of both mainstream and sidestream cigarette smoke from the NRC assessment of the

health effects of ETS.[17] The typical exposures in Table C-3 are consistent with the average concentrations of several airborne components of ETS measured in real indoor settings.

Using the NRC reported value for the average emission rate of respirable suspended particulate matter (RSP) per cigarette in sidestream smoke, 26 mg, EPA calculated a daily intake for passive exposure of 3 mg. Using the same methodology for 1,3-butadiene, with an emission rate of 400 ug per cigarette, one can calculate the average daily intake of a passive smoker to be 46 ug. This can be compared to an average daily intake of 16.4 ug for an individual exposed for 24 hours to the average ambient concentration of 0.37 ppbv (0.82 ug/m^3). Thus the typical exposure to 1,3-butadiene from passive smoking exceeds that of typical outdoor concentrations. GM recommends that calculations of 1,3-butadiene exposure from smoking and from passive exposure to ETS be included in Part A and in the Executive Summary to provide perspective for the reader.

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